Method Development in the Regioselective Glycosylation of Unprotected Carbohydrates

Niedbal, Dominika Alina

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

Method Development in the Regioselective Glycosylation of Unprotected Carbohydrates

Ph.D. Thesis

Dominika Alina Niedbal

August 2016

Department of Chemistry

Technical University of Denmark

Method Development in the Regioselective Glycosylation of Unprotected Carbohydrates

Ph.D. Thesis by Dominika Alina Niedbal

Acknowledgments

First, I would like to thank Professor Robert Madsen for supervising me during three years I have spent on the project and his help with practical and theoretical aspects of organic chemistry.

I would like to express my gratitude to the entire Madsen group and Department of Chemistry, both past and present members, for creating a good working atmosphere.

Special thanks to Gyrithe Lanz for being a great lab mate. It was a pleasure to share lab with you, discuss chemistry, life, and listen to good music.

I am very grateful to Tamara Lang and Andreas Ahlburg for proofreading this thesis.

The Novo Nordisk Foundation is acknowledged for financing my Ph.D. project.

Finally, I would like to thank my family and friends for their patience and support.

Dominika Niedbal

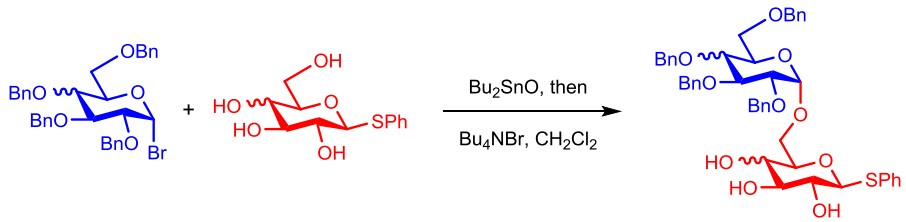
Kongens Lyngby, August 2016

Abstract

The present dissertation describes the research performed at the Technical University of Denmark in the period of February 2013 – January 2016 and involves a study on the tin- and boron-mediated glycosylation of unprotected carbohydrates.

Project 1: Tin-mediated glycosylation of unprotected hexopyranosides

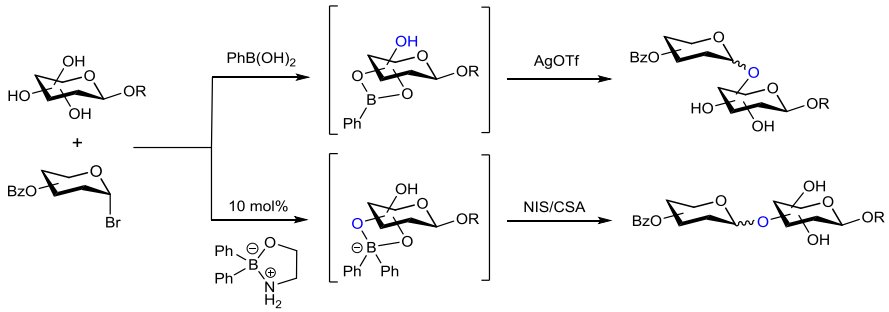
The regioselective glycosylation at the 6 position in 2,3,4,6-unprotected hexopyranosides has been investigated with dibutyltin oxide as the directing agent. Perbenzylated hexopyranosyl bromides were employed as the donors and the glycosylations were promoted by tetrabutylammonium bromide. The couplings were completely selective and gave rise to a number of 1,6-linked disaccharides with 1,2-*cis*-linked orientation.



Project 1 Tin-mediated glycosylation of unprotected hexopyranosides.

Project 2: Boron-mediated glycosylation of unprotected carbohydrates

Boron-mediated regioselective Koenigs-Knorr glycosylation has been studied with unprotected acceptors. By means of organoboron derivatives, *cis*-diols in acceptors can be either activated or masked via an ester formation.



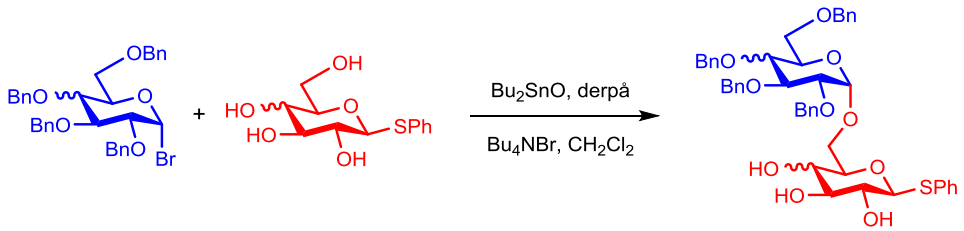
Project 2 Organoboron-mediated glycosylation of unprotected carbohydrates.

Resumé

Denne afhandling omhandler forskning, som er udført på Danmarks Tekniske Universitet i perioden februar 2013 – januar 2016 og beskriver undersøgelse af bor og tin medieret glykosylering af ubeskyttede kulhydrater.

Projekt 1 Tin medieret glykosylering af ubeskyttede kulhydrater

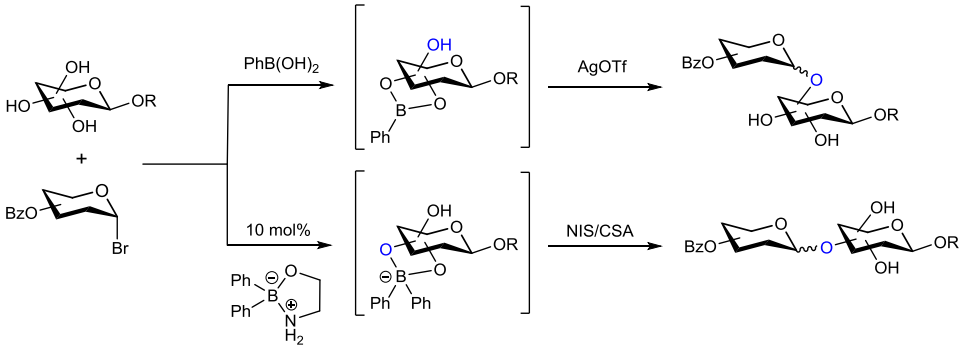
Regioselektive 6-*O*-glykosyleringer af ubeskyttede glycopyranosider med dibutyltin oxid er undersøgt. Denne glykosyleringsreaktion mellem tin aktiverede acceptorer og "armed" bromid donorer, under anvendelse af tetrabutylammonium bromid som promotorsystem, gav de tilsvarende (1→6) disakkarider i gode udbytter.



Projekt 1 Tin medieret glykosylering af ubeskyttede kulhydrater.

Projekt 2 Bor medieret glykosylering af ubeskyttede kulhydrater

Bor medieret regioselektiv Koenigs-Knorr glykosylering med ubeskyttede acceptorer er undersøgt. Organoborforbindelser kan enten aktivere eller blokere *cis*-dioler i acceptoren, og derfor hjælpe med regioselektiv og stereospecifik dannelse af den glykosidiske binding.



Projekt 2 Bor medieret glykosylering af ubeskyttede kulhydrater.

List of Abbreviations

Å	Angstrom
Ac	Acetyl
acac	Acetylacetonate
AgOTf	Silver triflate
Bn	Benzyl
BTF	Benzotrifluoride
Bu	*n*-Butyl
Bz	Benzoyl
CSA	Camphorsulfonic acid
d	Doublet (spectral)
DAST	Diethylaminosulfur trifluoride
DCE	1,2-dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
DMTST	Dimethyl-(methylthio)-sulfonium triflate
DTBPI	2,6-di-*tert*-butyl pyridinium iodide
equiv	Equivalent(s)

Et	Ethyl
Et_2O	Diethyl ether
Et_3N	Triethylamine
Gal	Galactoside
Glc	Glucoside
h	Hour(s)
HMBC	Heteronuclear multiple-bond correlation
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation
IDCP	Iodonium dicollidine perchlorate
IR	Infrared spectroscopy
J	Coupling constant
LG	Leaving group
m	Meta
m	Multiplet (spectral)
Me	Methyl
MS	Molecular sieves
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
NPG	Non-participating group
o	Ortho
p	Para
Pent	*n*-Pentenyl

PG	Participating group
Ph	Phenyl
Phth	Phthalimido
ppm	Parts per million
rt	Room temperature
RVC cathode	Reticulated Vitreous Carbon cathode
s	Singlet (NMR)
SET	Single-electron Transfer
t	Triplet (NMR)
TBAHS	Tetrabutylammonium hydrogen sulfate
TBDMSCl	*tert*-Butyldimethylsilyl chloride
TBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
Tf	Trifluoromethanesulfonyl
TfO-	Trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSI	Trimethylsilyl iodide
TMU	1,1,3,3-tetramethylurea
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Tol	Tolyl
UV	Ultraviolet

Publications

- Publication Included in the Appendix

“Halide-mediated regioselective 6-O-glycosylation of unprotected hexopyranosides with perbenzylated glycosyl bromide donors”

Table of Contents

1 Aim of the project

Accessing a large number of well-defined oligosaccharides is important for future developments in the field of glycobiology. Through the years, many synthetic methods were proposed, but assembly of complex glycans remains a time-consuming and complicated process. The development of easier, cheaper and more efficient methods is a main goal in the carbohydrate chemistry field.

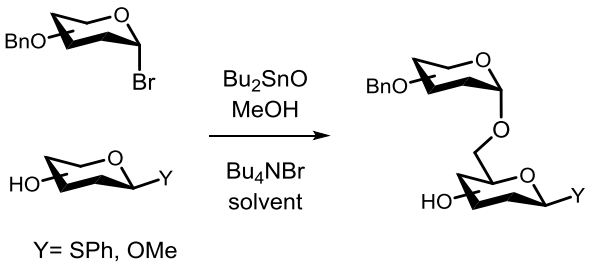
The main restriction in oligosaccharide synthesis is the extensive use of protecting groups. In that way the problem of regioselective glycosylation has been addressed throughout the years. Use of protecting groups suppresses glycosylation at undesired positions but additional steps are required to install and remove the protecting groups.

In recent years, numerous procedures to avoid or decrease protecting group manipulations have been developed. Several of these procedures use certain metals or metalloids, such as tin or boron, to coordinate diols and increase the reactivity differences between the hydroxyl groups in sugars. Although some successful investigations in tin- and boron-mediated glycosylations have been done, there is still room for a more extensive study in this area.

In this study, stannylene-mediated glycosylations are further investigated by coupling unprotected acceptors with armed halide donors in the Lemieux procedure, as shown in Scheme 1a.

Boron-mediated coupling is also explored by means of boronic, as shown in Scheme 1b and borinic acids, shown in Scheme 1c, in Koenigs-Knorr type glycosylations, where silver triflate (AgOTf) and *N*-iodosuccinimide/camphorsulfonic acid (NIS/CSA), respectively, are used as promoter systems. Two minor projects concerning testing copper salts as a promoting system in the glycosylation, shown in Scheme 1d and the synthesis of unprotected halide donors are also described.

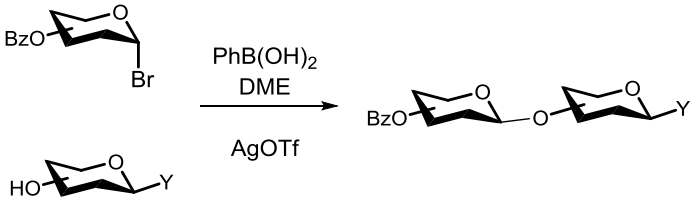
a)



Y= SPh, OMe

---

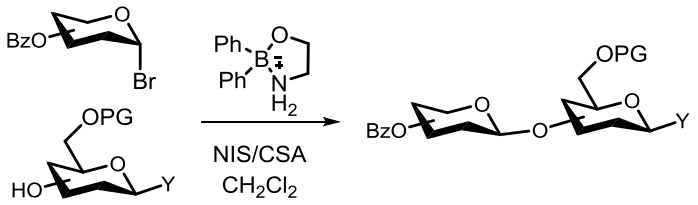
b)



Y= SPh, OMe

---

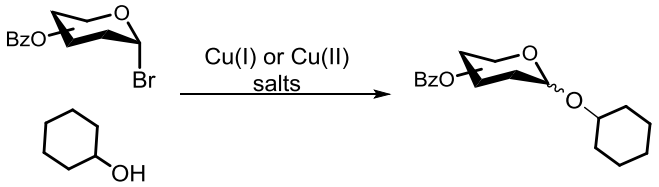
c)



Y= SPh, OMe

---

d)



Scheme 1 Projects described in the study.

2 Introduction

Carbohydrates are one of the most important biomolecules on Earth. Even though our knowledge about these compounds still needs to be deepened, we have already learned about some carbohydrate involvement in damaging cellular processes *e.g.* development and growth of tumors[1], metastasis[2] or viral and bacterial infections, as shown in the example in Figure 1.[3]

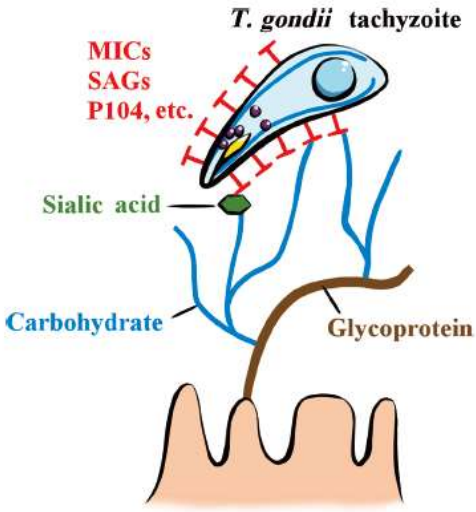


Figure 1 Schematic image of enteric pathogen (in this case T. gondii) invasion showing proteins attached to carbohydrates on host cells.[3]

The great medicinal potential of glycomolecules has already been proven by the development of synthetic carbohydrate-based therapeutic agents.[4] Further explanation of carbohydrate-involved mechanisms would be easier, if detailed information about structure, properties and conformation of the glycostructures were available. For that reason, the improvement of methods for the isolation and synthesis of complex carbohydrates has become crucial for the glycoscience field.

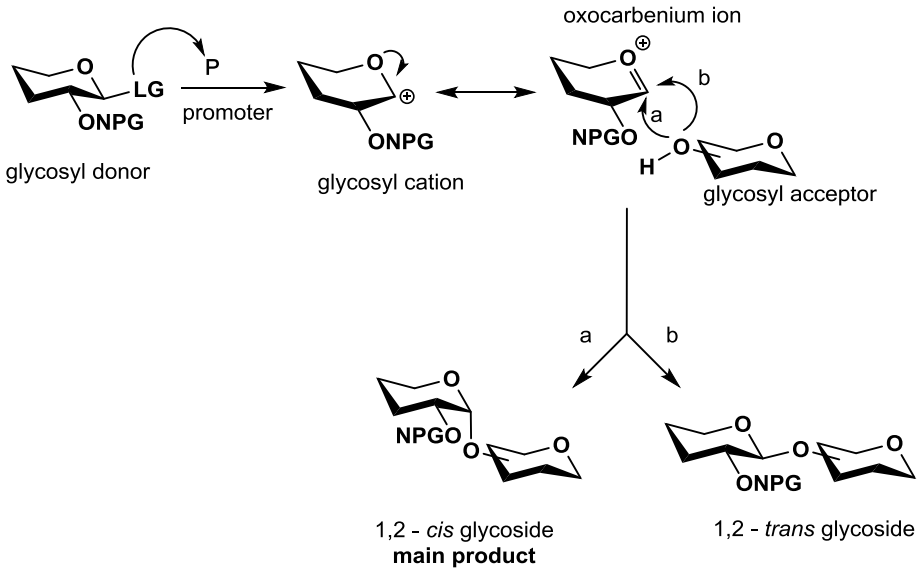
The majority of carbohydrates in nature exist as polysaccharides (cellulose, starch, chitin) or glycoconjugates (glycopeptides, glycolipids) in which monosaccharides are connected via glycosidic linkages.

The reaction performed to connect two monosaccharide units is the glycosylation reaction. During recent years, significant development in oligosaccharide synthesis

has been observed. Despite this progress, there are still problems with the direct access to some challenging glycosidic linkages.

One of the most difficult aspects is the inability to predict and control regioselectivity of the glycosylation. For many years, optimization of this reaction has remained fundamental in the carbohydrate chemistry field. Especially now, when the glycobiology field is expanding, there is a need for reliable and stereocontrolled glycosylation methods.

In Scheme 2 the commonly accepted mechanism of the glycosylation is shown. Scheme 2a shows the glycosyl donor with a non-participating group at C2 and Scheme 2b the glycosyl donor with a participating group.

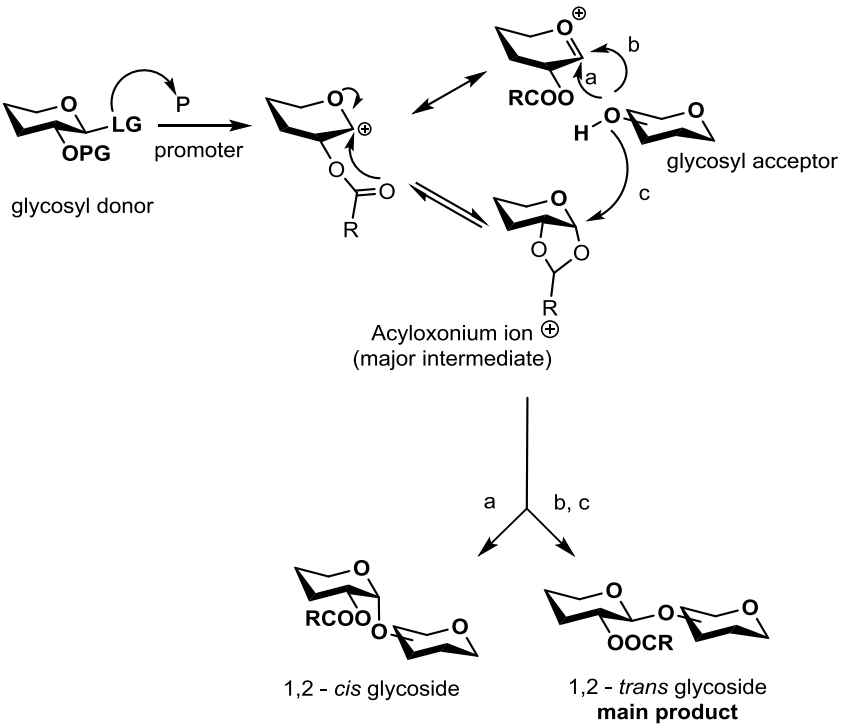


Scheme 2a Mechanism of glycosylation without neighboring participating group at C-2.

In the first step, an electrophilic promoter activates the nucleophilic leaving group (LG), employed at the anomeric carbon of a glycosyl donor. The departure of the anomeric LG results in formation of the glycosyl cation. Intramolecular stabilization of the glycosyl cation in the glycosyl donor bearing a non-participating group proceeds by resonance from O-5, which results in the oxocarbenium ion formation. Very recently, this oxocarbenium ion was detected by NMR spectroscopy in a highly acidic media.[5] The most frequently used nonparticipating groups are benzyl for hydroxyl groups and azide for amino groups. The anomeric carbon of both resonance contributors is sp^2 hybridized and therefore the nucleophilic attack is possible either

from the top (*trans*) or from the bottom (*cis*) of the ring. Even though the α-product is thermodynamically favored because of the anomeric effect, a significant amount of kinetic β-linked product is often obtained.

Scheme 2b illustrates the formation of the 1,2-*trans* glycosidic linkage with the use of neighboring participating group.



Scheme 2b Mechanism of glycosylation with neighboring participating group at C-2.

The most commonly used participating groups are acyl moieties: *O*-acetyl, *O*-benzoyl or 2-phthalimido groups. The glycosylation proceeds predominantly via the acyloxonium ion, formed as a result of the promoter-assisted departure of the LG followed by the intramolecular stabilization of the glycosyl cation. The attack of a nucleophile is only possible from the top face of the ring, leading to the stereoselective formation of a *trans* glycoside.

In both cases, the glycosylation may lead to a mixture of the 1,2-*cis* and the 1,2-*trans* glycosides. Formation of the glycosidic linkage is the key step in oligosaccharide synthesis and number of factors have to be considered while performing the glycosylation reaction:

- Configuration of glycosyl donor
- Nature of protecting groups of the donor (armed-disarmed)
- Type of the leaving group
- Type of the promoter used for activation
- Selected solvent
- Type of the selected glycosyl acceptor

A number of functional groups employed for glycosyl donors are commonly known. The most popular glycosyl donors are thioglycosides, imidates, phosphates, 4-pentenyl glycosides and glycosyl halides. In the next paragraphs, these donors will be described more extensively with stronger focus on halides and thioglycosides, since they were employed in this research as donors in both the Lemieux[6] and the Koenigs-Knorr[7] glycosylation. The armed-disarmed concept and the anomeric effect will be also shortly explained.

2.1 Anomeric effect

In cyclohexanes, equatorial substituents are energetically favored because of 1,3-diaxial interactions occurring for substituents in axial positions. Thus, D-glucopyranose should be expected to form the β-anomer, in which all substituents are equatorially oriented in the $^4C_1$ conformation. However, in aqueous solution, both the α- and β-anomers are present and that suggest presence of another operating effect that competes successfully with the above-mentioned destabilizing one. Other polar substituents like halides, -OR and –SR attached to the anomeric center of pyranosides favor the axial orientation. This phenomenon was discovered and named the "anomeric effect" by Raymond Lemieux.[8, 9] In general, the effect is valid for all molecules with at least two heteroatoms linked to a tetrahedral center like C-X-C-Y, where X=N, O, S and Y=Br, Cl, N, O or S.

Two alternative explanations for the origin of anomeric effect exist. The first one is a dipole-dipole interaction and the second one is a stereoelectronic effect, where both are shown in Figure 2:

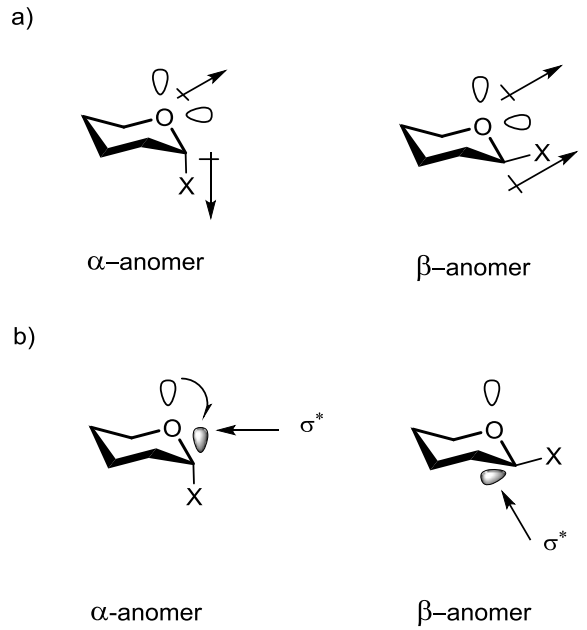


Figure 2 a) Dipole moment in the α- and β-anomers; b) Lone pair and σ* orbitals and their orientation in α- and β-anomers.

In both cases depicted above the two nonbonding electron pairs on the endocyclic sp^3 hybridized oxygen atom play an important role. They form the dipole, which is pointing in the exocyclic direction. Another dipole is formed between the anomeric carbon and the exocyclic heteroatom attached to it. In the β-anomer, the two dipoles are practically parallel to each other and interaction of these two dipoles is energetically unfavored.

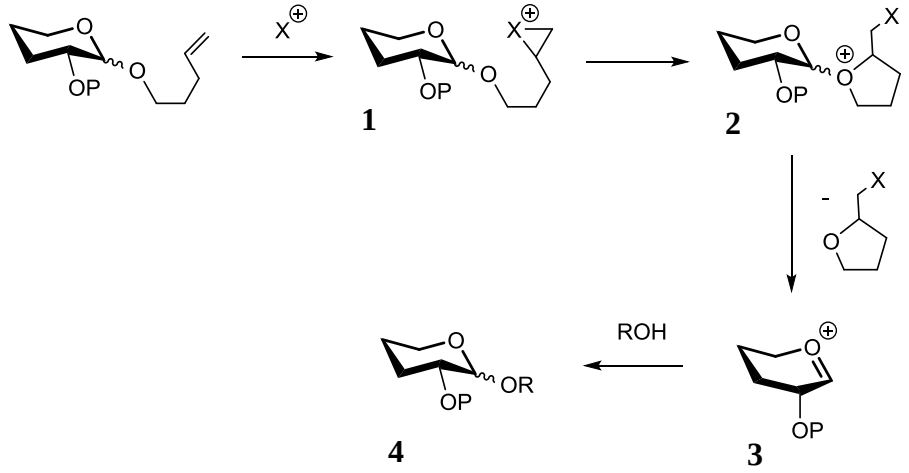
In the α-anomer, the two dipoles point in different directions and the dipole-dipole interaction is small.

The stereoelectronic interpretation assumes that the nonbonding electrons of the endocyclic oxygen atom are synperiplanar to the antibonding orbital of the anomeric substituent when it is in the axial position. Consequently, the two orbitals can mix and form a n-σ* interaction, which results in the shortening of the endocyclic oxygen-anomeric carbon bond and the lengthening of the anomeric carbon-heteroatom substituent bond, only when the substituent is in the axial position in the $^4C_1$ conformation.

2.2 Glycosyl donors

2.2.1 *n*-Pentenyl glycosides

n-Pentenyl glycosides have been introduced by Fraser-Reid and co-workers[10] in 1988. This type of glycosyl donor provides very good stability under a wide range of protecting group manipulations. In Scheme 3 activation and further glycosylation of *n*-pentenyl donors is shown.



Scheme 3 Glycosylation with *n*-pentenyl glycosides.

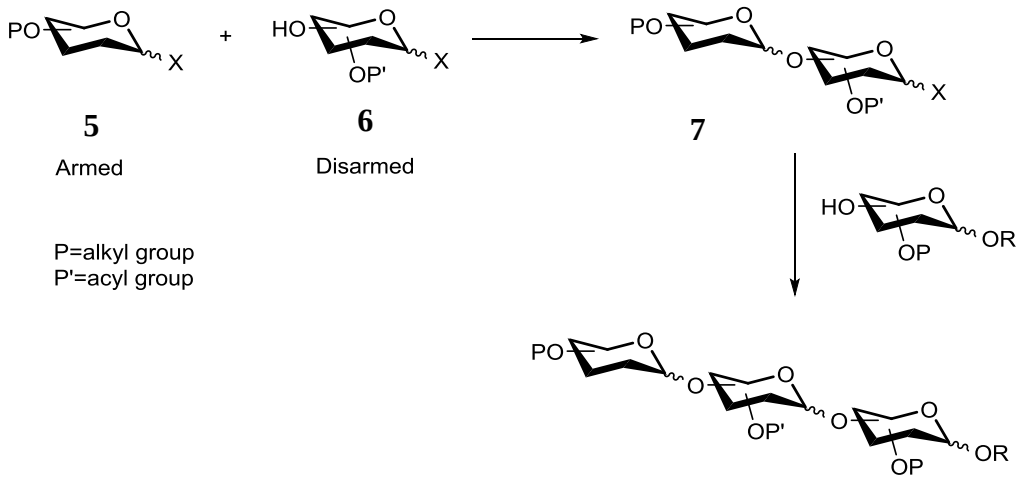
n-Pentenyl glycosides are activated by halogenation of the double bond (as in **1**) and this results in cyclization (as in **2**) and the release of the aglycone (as in **3**). Consequently, the active glycosylating species is formed (i.e. **4**). The most popular promoters for these glycosylation reactions are NIS/TfOH, NIS/TESOTf or iodonium dicollidine perchlorate (IDCP).

During studies on *n*-pentenyl glycosides, a major difference in the reactivity of benzyl protected species compared with the acetylated counterparts was discovered. In detail, the acetylated derivatives were reacting much slower. This observation gave rise to the development of the armed-disarmed concept, in which an acetylated *n*-pentenyl glycoside (disarmed) with a free primary position could be glycosylated with a benzylated *n*-pentenyl glycoside (armed) without self-condensation of the acetylated species.

2.2.1.1 Armed-disarmed approach

As mentioned above, armed-disarmed glycosylations have been introduced by Fraser-Reid and co-workers.[11,12] In this strategy, only one type of anomeric group is used. The approach is based on the observation that the substituents in the sugar ring can influence the reactivity in the glycosylation, which predominantly relates to those at C-2. Generally, electron-withdrawing groups, such as acyl groups, disarm the glycosylation capability, while electron-donating groups, such as ethers arm the anomeric center.

As shown in Scheme 4, an armed donor **5** undergoes a reaction with a disarmed acceptor **6** without self-condensation of the latter. The newly formed compound **7** is disarmed but can be used as a glycosyl donor in a further coupling. Further use requires either arming it by exchanging protecting groups or by using a more powerful promoter that is capable of activating the disarmed species.



Scheme 4 Armed-disarmed glycosylation.

Originally the armed-disarmed approach was described for *n*-pentenyl glycosides[11] but later it was found out that the phenomenon is quite common. Armed-disarmed glycosylations with various donors were reported, including glycosyl fluorides[13], thioglycosides[14] or hemiacetals.[15]

The chemoselective activation principles have been expanding throughout the years, and therefore, a database of relative reactivity values (RRVs) has been created[16] and some important observations have been made:

- Among commonly protected pyranosides (e.g.: perbenzylated), reactivity decreases in the following order: fucose > galactose > glucose > mannose > sialic acid, although the differences are not significant.[17]
- For galactose, the C2 substituent plays an important role in deactivating the pyranose. Reactivity is reduced the most by groups listed in the following order: OClAc > OBz > OAc > NHTroc > OBn > > OH > OSilyl > H.[17]
- The position that mostly affects the reactivity of pyranosides is not the same for all monosaccharides. For example the C2 position has the greatest effect on the reactivity for mannose (followed by C6>C4>C3)[18] while for galactose the order is C4 > C3 > C2 > C6. [16,17]
- Torsional effects: substituents in axial position increase reactivity of thioglycoside donors.[19]
- Influence of the leaving group:
  Steric effect: changing the size of the anomeric group can change the reactivity of the glycosyl donor. The influence of steric effects of thioglycosides on glycosyl reactivity was studied by Boons and co-workers[20] and showed that more bulky groups reduce the reactivity;
  Electronic effect: the reactivity of the phenyl thioglycoside donor can be influenced by the nature of the substituent in the para position of the phenyl ring with following order: OMe > H > NO_2.

Later the concept was expanded by introducing additional approaches like orthogonal glycosylation strategy[21] or active-latent glycosylations,[22] but they will not be discussed in this thesis in further detail.

2.2.2 Glycosyl imidates

The first description of glycosyl acetimidates comes from 1976 from Sinaÿ and co-workers.[23] Further development of the original imidate procedure by Schmidt *et al.*[24] led to the introduction of trichloroacetimidates and 20 years later, trifluoroacetimidates were introduced.[25] The donors are shown in Figure 3 in the order of the development.

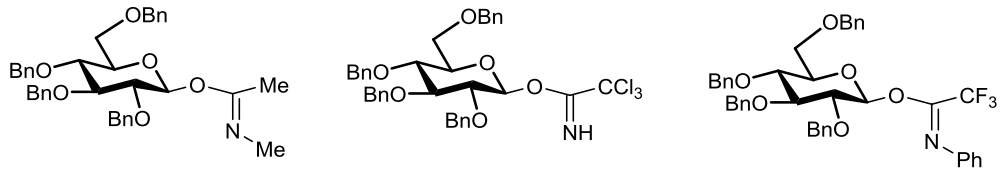


Figure 3 From left example of: acetimidate, trichloroacetimidate and trifluoroacetimidate.

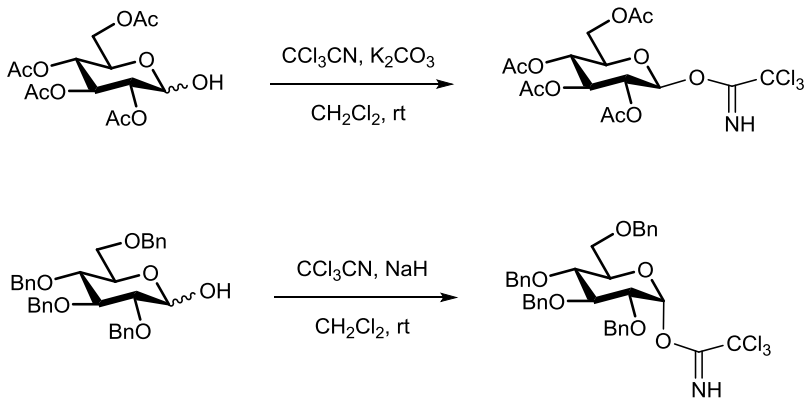
The most widely used imidates in modern carbohydrate chemistry are trichloroacetimidates. They can be easily prepared by a base-catalyzed addition of an anomeric hydroxyl group to trichloroacetonitrile using both organic and inorganic bases. Later in the glycosylation, only a catalytic amount of a Lewis acid is used as a promoter.[26]

Trichloroacetimidates show excellent donor properties regarding stability, reactivity and ease of formation. Moreover, they usually result in high product yields and high anomeric stereocontrol.[26]

Both acetimidates and trifluoroacetimidates did not show the same good properties as trichloroacetimidates. *O*-Glycosyl-*N*-methyl acetimidates required extensive preparation and showed low reactivity and trifluoroacetimidates were also less efficient in terms of product yields.[27]

However, in specific cases acetimidates and trifluoroacetimidates could work efficiently. The acetimidates react in the presence of *p*-toluenesulfonic acid as a promoter to give 1,2-*cis*-glycosides with very good stereoselectivity.[28] On the other hand, trifluoroacetimidates could be efficiently activated by the I_2/Et_3SiH promoter system.[29]

As mentioned above, trichloroacetimidates can be formed under basic condition. However, depending on the strength of the base axial and equatorial imidates can be formed, as shown in Scheme 5.

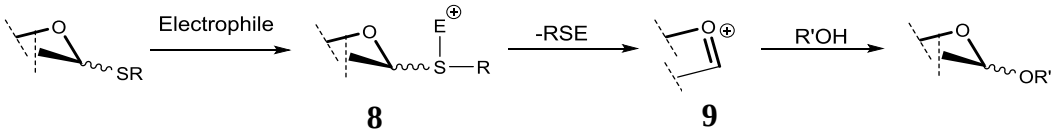


Scheme 5 Conditions for trichloroacetimidate formation.

Generally, in the presence of a weak base, such as potassium carbonate, the equatorial imidate as a kinetic product can be isolated. When a stronger base is used, e.g. sodium hydride, the thermodynamically more stable axial imidates are formed. Trichloroacetimidates are quite stable under neutral or basic conditions, but react readily in the presence of acids. Various acidic nucleophiles, like carboxylic acids form glycosyl esters without additional catalysts. Reaction with non-acidic *O*-nucleophiles proceeds in the presence of Lewis or Brønsted acids. Currently, TMSOTf and $BF_3 \cdot Et_2O$ are the most often used promoters and glycosylations with these are carried out at low temperatures under mild conditions.[27]

2.2.3 Thioglycosides

Thioglycosides are one of the most frequently used glycosyl donors in oligosaccharide synthesis. In general, they show several advantages over other glycosyl donors namely that they have long shelf lives and that they tolerate very diverse chemical manipulation, leaving the thioglycoside function intact. Furthermore, thioglycosides are inert under several glycosylation conditions, so they can act as glycosyl acceptors in the synthesis. Lastly, they are cheap to prepare and can be activated under mild conditions by thiophilic reagents, usually soft electrophilic reagents, as shown in Scheme 6.[30]



Scheme 6 Activation of thioglycosides.

Thioglycosides activated by the electrophile form a sulfonium ion **8** that is a better leaving group and therefore loss of the sulfonium ion with the assistance of the ring oxygen leads to the common intermediates of the glycosylation reaction (i.e. **9**). The oxocarbenium ion **9** will then react with the *O*-nucleophile to produce *O*-glycosides.

In 1973 Ferrier and co-workers[31] reported the first synthesis of a disaccharide with a thioglycoside as the donor, where mercury (II) sulfate was used to promote the reaction. Throughout the years, the need for less toxic glycosylation conditions was in demand, so improvement in activation conditions with new promoters has become a subject of research since then.[32] Figure 4 presents promoters capable of generating thiophilic species, categorized in four major types: (1) metal salts; (2) halonium reagents; (3) organosulfur reagents; (4) single electron transfer methods.

Thiophilic metal salts, including Cu^{2+}, Hg^{2+}, Ag^{+} salts, have been used in the beginning as promoters for glycosylation of thioglycoside donors.[33, 34, 35, 36, 37, 38] These heavy metal salts are toxic and demand appropriate disposal, especially when used in stoichiometric amounts. By the present standard, activation of thioglycosides with these promoters require harsh conditions. Moreover, complex by-products are commonly accompanying the reaction.

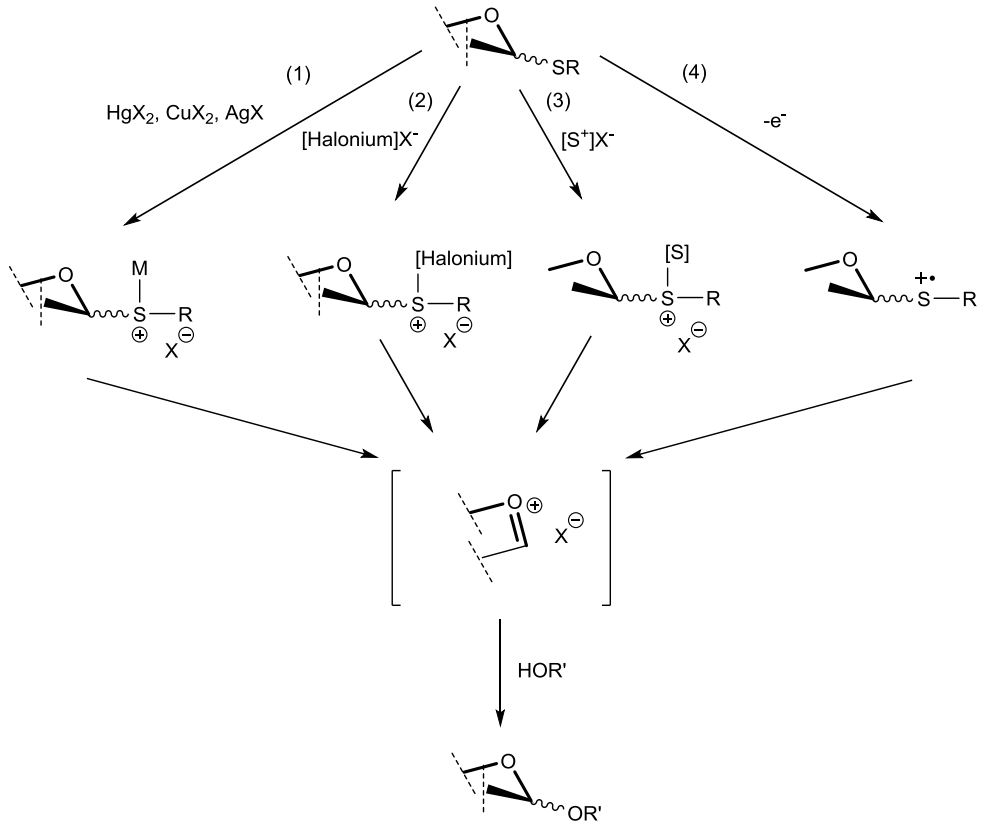
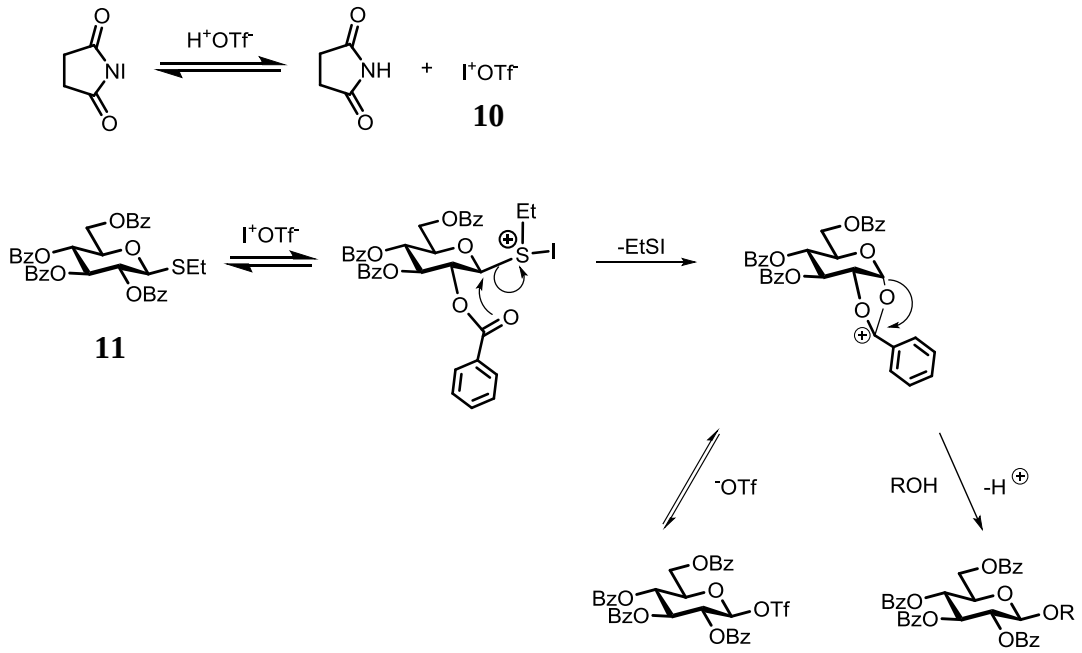


Figure 4 Ways of generating thiophilic species.

In the Ferrier work mentioned above, the reaction was reproducible 'only when freshly prepared mercuric sulfate was used' and as a result, heavy metal salts are nowadays very rarely used in the glycosylation of thioglycosides.

Bromonium and iodonium species can promote 1-thioglycosides to undergo glycosylation under milder conditions, because they are more electrophilic than heavy metal salts. In 1983 Nicolaou and co-workers reported *N*-bromosuccinimide as a promoter in the glycosylation of thioglycosides.[39] It was not until 1990 that NIS/TfOH and NIS/AgOTf, currently the most frequently used promoters, were discovered by research groups of Fraser-Reid[40] and van Boom.[41] In Scheme 7, the mechanism with NIS/TfOH activation is shown.



Scheme 7 Mechanism of NIS/TfOH activation.

The reaction starts with the formation of iodonium ion **10**, which is more electrophilic than NIS. Then, the iodonium ion activates the thioglycoside **11**, resulting after a cascade of events, in the continuous regeneration of TfOH and in this way illustrating the catalytic role of triflic acid in the glycosylation.

Before thioglycosides were directly used as donors in the glycosylation, they were converted to glycosyl bromides. Kihlberg and co-workers[42] reported Br_2/AgOTf or Br_2/$Hg(CN)_2$ as promoters for the glycosylation of thioglycosides, in the way that thioglycosides are converted into the corresponding bromides and the bromides are then undergoing a glycosylation process. Later, thioglycosides could be converted into glycosyl iodides or chlorides followed by *in situ* glycosylation by means of I_2[43, 44, 45] and ICl or IBr/ AgOTf.[46]

The third major type of promoters are organosulfur reagents, which is a widely used group of promoters used in thioglycoside glycosylation. In 1986, Garegg and co-workers discovered dimethyl(thiomethyl)sulfonium triflate (DMTST) as a powerful promoter for thioglycosides activation.[47, 48] Since then, many organosulfur promoters have been described in the literature and have found application in the field, for example MeSOTf[49] or sulfinyl derivatives in the presence of Tf_2O.[50] The last class of thioglycoside promoters is an oxidative activation process via a single electron

transfer mechanism, which was first reported by Amatore/Sinaÿ and Lubineau.[51, 52] Oxidation of a thioglycoside leads to the S-radical cation, which collapses to a thiyl radical and a glycosyl oxocarbenium species that then undergoes glycosylation. Besides the electrochemical approach mentioned before, a few SET reagents have also been applied to the glycosylation of thioglycosides.[53]

2.2.4 Glycosyl halides

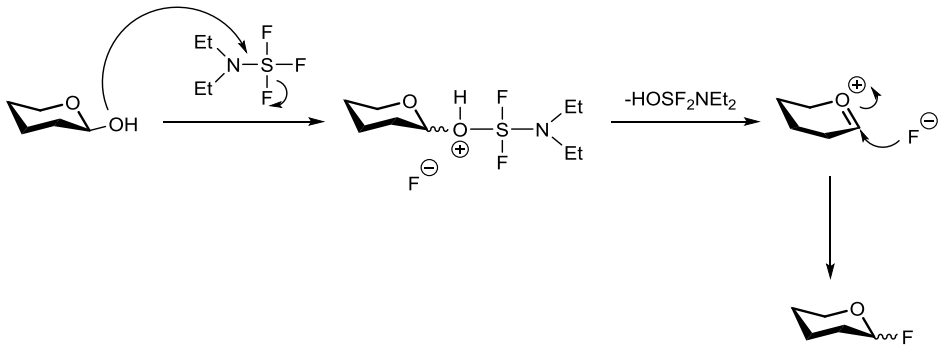
Halides follow the same reactivity order in glycosylations as in nucleophilic substitutions, i.e. F<Cl<Br<I. They have been widely applied in stereoselective *O*-glycosylations, nucleophilic displacement and radical reactions.
In the synthesis of oligosaccharides glycosyl bromides have been one of the most popular donors since the first reported glycosylation.[7] Glycosyl fluorides have been for a long time believed too stable to be used in the glycosylation. Glycosyl chlorides, due to their reduced activity, have limited applications. On the contrary, glycosyl iodides have been for a long time perceived as too reactive to be useful donors.

2.2.4.1 Glycosyl fluorides

Glycosyl fluorides cannot be activated under standard Koenigs-Knorr conditions, because of their low reactivity. Therefore, use of glycosyl fluorides as donors was developed after the glycosyl bromides and Mukaiyama *et al.* first introduced them in 1981.[54]
When it was discovered that a weak Lewis acid, stannous chloride, could activate the C-F bond of glycosyl fluorides, the method was highly desirable due to the many advantages of fluoride donors:

- The ease of preparation under mild conditions
- A diversity of suitable promoters available for coupling with glycosyl acceptors
- Comparatively high stability towards silica gel chromatography
- Ease of monitoring the reaction of fluorides by NMR spectroscopy
- Application to the armed-disarmed concept for convergent synthesis of oligosaccharides

The most common method for glycosyl fluoride preparation is the reaction of a protected sugar with a free anomeric hydroxyl group with diethylaminosulfur trifluoride (DAST) and the reaction is shown in Scheme 8. When a benzylated D-glucose derivative is treated with DAST in THF at low temperature, the corresponding fluoride is produced in excellent yield and with high β-selectivity.

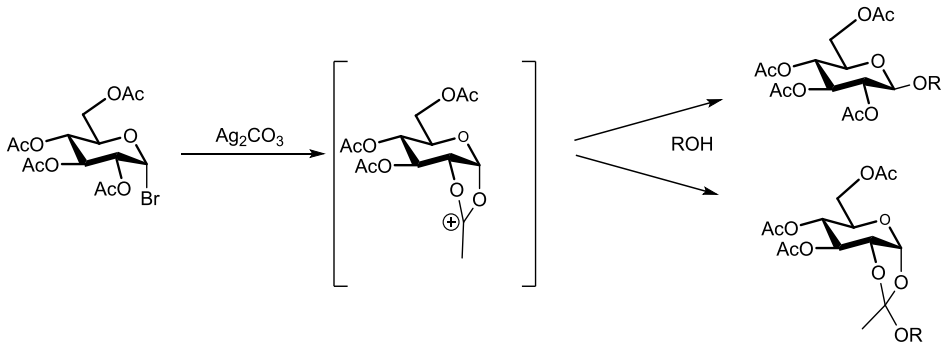


Scheme 8 Synthesis of glycosyl fluorides with the use of DAST.[55]

A very important feature of glycosyl fluorides is that they can be activated under specific conditions that most protecting groups survive. Mukaiyama used the combination of $SnCl_2$ and $AgClO_4$ and later Suzuki employed Cp_2HfCl_2 and $AgClO_4$.[56] Over the past 30 years, many other promoters were introduced, such as SiF_4 and TMSOTf[57], $BF_3{\cdot}Et_2O$[58, 59] or Tf_2O.[60]

2.2.4.2 Glycosyl bromides

The popularity of glycosyl bromides is mostly connected to the Koenigs-Knorr reaction, published in 1901.[7] The original Koenigs-Knorr method is a synthesis of glycosides with glycosyl bromides or chlorides and alcohols in the presence of the promoter Ag_2CO_3. However, generally glycosyl bromides are preferred over the chlorides in this glycosylation. As shown in Scheme 9, the product of the reaction, due to the participating acetyl group at C-2 in the peracetylated glucopyranosyl bromide, is the 1,2-*trans* glycoside.



Scheme 9 Koenigs-Knorr glycosylation.[61]

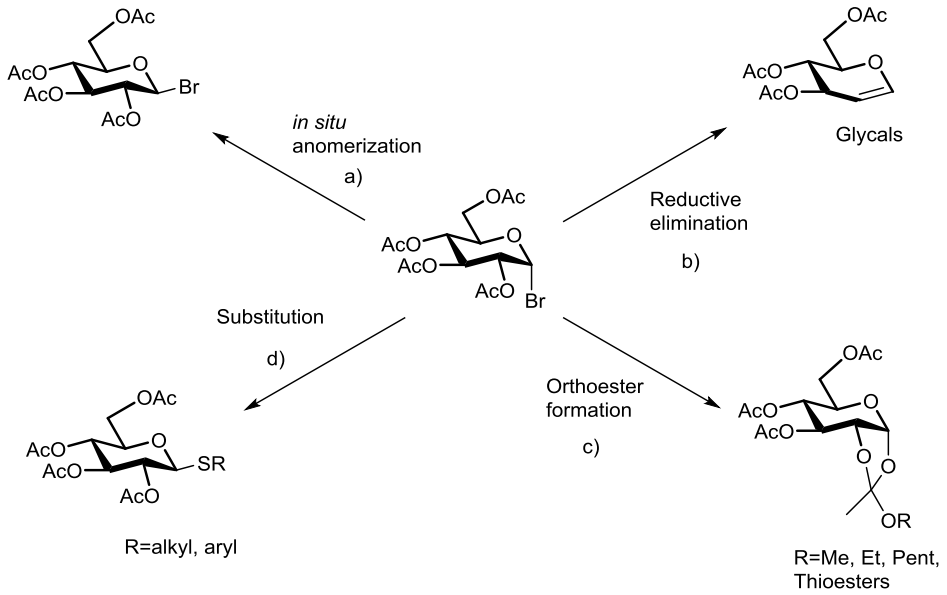
Involvement of the neighboring group leads to the formation of the acyloxonium ion, which shields one side of the anomeric center, so the anomeric carbon can only be attacked by the nucleophile from the other side. Later it was found out that during the Koenigs – Knorr glycosylation orthoesters can be formed.[61]

After Ag_2CO_3, Ag_2O was introduced as a promoter in the glycosylation. The drawback of using these silver salts is that water is generated during the reaction and yields are low. Yields can be improved by adding drying agents such as molecular sieves to the reaction mixture.

Over the years more promoters were introduced, such as $Hg(OAc)_2$ by Zemplén[62], $Hg(CN)_2$ and $HgBr_2/Hg(CN)_2$ by Helferich[61, 63] and the most important AgOTf.[64]

The latter has also been used successfully in Robert Madsen's group in the glycosylation of unprotected carbohydrates with phenylboronic acid as a transient protecting group.[65]

In addition to the *O*-glycosylation reaction, glycosyl bromides can also be converted to other compounds that can have different applications, as shown in Scheme 10.[66]



a) Bu_4NBr, CH_2Cl_2
b) Zn, CH_3COOH or RVC catode, zinc anode, $LiClO_4$, THF
c) KF, EtOH, CH_3CN
d) thiophenol, TBAHS, Na_2CO_3, CH_2Cl_2

Scheme 10 Conversion of glycosyl bromides into other synthetically useful species. [67, 68, 69, 70]

Acetylated α-glycosyl bromides can be converted into glycals via reductive elimination e.g., with Zn metal[70] or under a simple electrochemical setup.[67] Glycosyl bromides can also form 1,2-orthoesters in the presence of sterically hindered base or by using potassium fluoride in acetonitrile.[68]

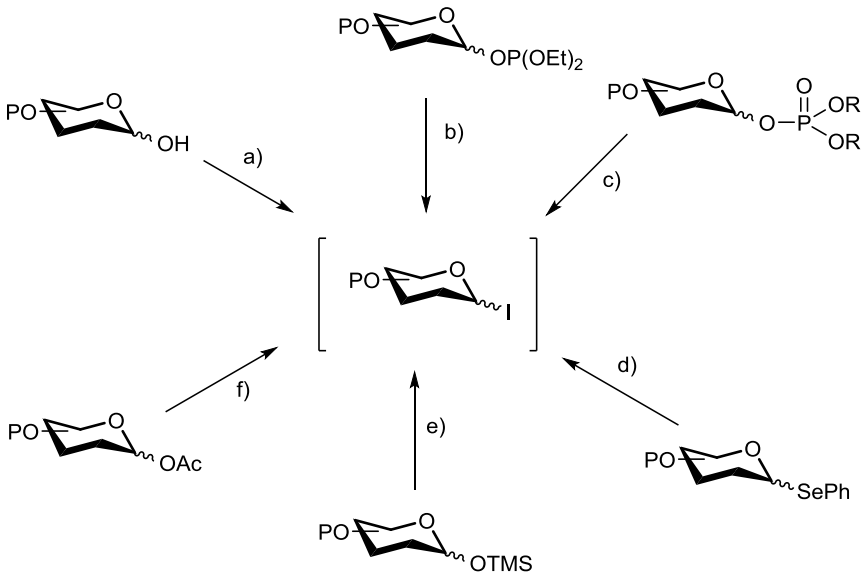
Anomeric bromides can be converted into other important glycosyl donors such as 1,2-*trans* thioglycosides.[69]

Lastly, glycosyl bromides are also undergoing *in situ* anomerization, which will be described more extensively in the next paragraphs.

2.2.4.3 Glycosyl iodides

In recent years, glycosyl iodides have gained significant popularity in the synthesis of carbohydrates. Until then they have been used only occasionally as glycosyl donors due to their instability. During closer studies, it was found out that the reactivity and stability of iodides can be tuned by changing the protecting group pattern. In this way, per-*O*-silylated iodides that are generated in situ are very reactive, partly benzylated iodides are moderately reactive and can be stored for a long time in temperatures beneath zero, while per-*O*-acetylated iodides are stable crystalline solids with long shelf lives.[71]

Glycosyl iodides were first prepared by Helferich in the reaction of glycosyl bromides with sodium iodide in acetone.[72] Since then, several methods of installing iodide in the anomeric position have been published, as shown in Scheme 11. Method **a** describes anomeric hemiacetals with diverse protecting groups (Bz, Bn, Ac) that upon treatment with a polymer-assisted triphenylphosphine–iodine complex and imidazole can be converted into α-glycosyl iodides.[73] Another method, **b**, originates with per-*O*-benzylated glycosyl diethylphosphites (D-Glc, D-Gal, L-Fuc). They have successfully been applied to generate glycosyl iodides using 2,6-di-*tert*-butyl pyridinium iodide (DTBPI) in CH_2Cl_2 at room temperature.[74] Method **c**, called the Waldmann's method, employs per-*O*-benzylated glycosyl phosphates as precursors to glycosyl iodides. Glycosyl iodides are generated by the reaction of LiI in 1 M solution of $LiClO_4$ in CH_2Cl_2 or CH_3CN.[75] In the method **d**, selenoglycosides provide the corresponding iodides upon treatment with molecular I_2. NMR studies showed that armed selenoglucosides are quickly converted into the corresponding iodides, while the disarmed counterparts are converted during four days.[76] Method **e** describes acetylated monosaccharides that can also be transformed into glycosyl iodides by means of HI treatment that is generated *in situ* in the reaction of I_2 and triethylsilane.[77]

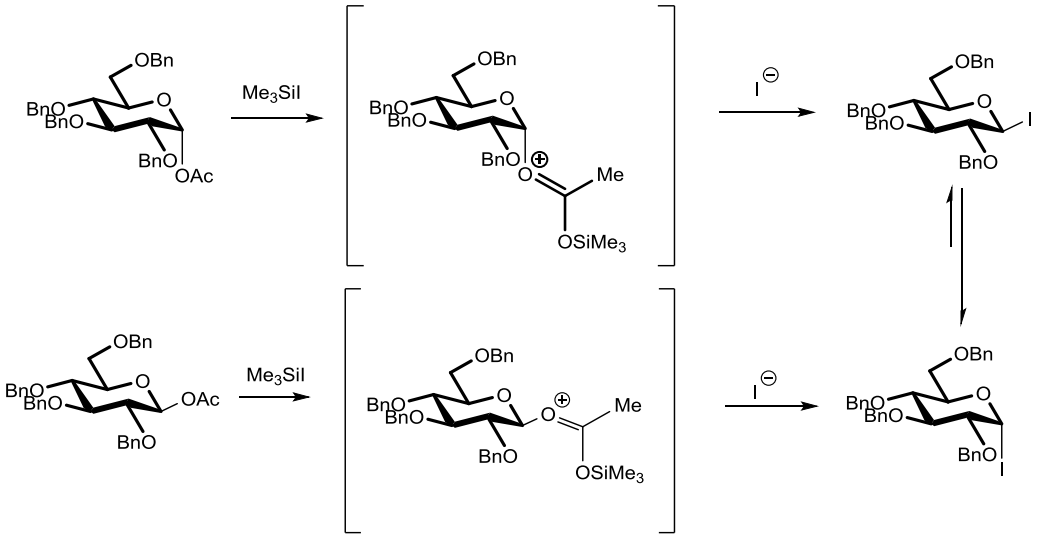


a) -C_6H_4-PPh_2-I_2, Imidazole
b) DTBPI, 4Å MS, CH_2Cl_2
c) 1M $LiClO_4$, LiI, 4Å MS, CH_2Cl_2
d) I_2, $CDCl_3$
e) TMSI or I_2/Et_3SiH or HI
f) TMSI, CH_2Cl_2

Scheme 11 Different ways of glycosyl iodide synthesis. [73, 74, 75, 76, 77, 78, 79, 80]

Method **f** is so far one of the most popular methods for glycosyl iodide formation. In 1980 Thiem and Meyer reported that glycosyl acetates, methyl glycosides and 1,6–anhydrosugars are undergoing reaction with trimethylsilyl iodide (TMSI) to form α-glycosyl iodides.[78]

The most important reaction of glycosyl iodides is α-selective glycosylation via *in situ* anomerization. The reaction was established by Gervay-Hague and co-workers.[79] By using the same protocol they later published mechanistic studies on the stereoselective formation of glycosyl iodides involving first characterization of β-iodides, as shown in Scheme 12.[80]



Scheme 12 Proposed mechanism of glycosyl iodide formation[80].

Armed glycosyl iodides undergo the anomerization reaction in the presence of tetrabutylammonium iodide (TBAI) and diisopropyl ethylamine (DIPEA), known as Hünig's base, with different acceptors. Under these conditions, the α-iodide is first formed, which undergoes attack by iodide to generate the thermodynamically unstable β-iodide. The β-iodide, as a more reactive species than the corresponding α-iodide, reacts with nucleophilic acceptors to form α-glycosides. The only by-product in this reaction is the volatile trimethylsilyl acetate.

2.3 1,2-*cis* *O*-glycosylations

The importance of the stereoselective formation of a 1,2-*cis* glycosidic bond comes from the natural existence of many 1,2-*cis*-linked glycosides, glycoconjugates, poly- and oligosaccharides that are extensively distributed in living tissues. The biological role and therapeutic potential of these compounds have gained great interest over the past 20 years.[81,82, 83,84,85] One of the disadvantages is the low availability of pure samples from natural sources. Chemical synthesis would allow access to substantially larger amounts of pure material.

As described in the previous paragraph, 1,2-*trans* glycosides can be commonly prepared with the assistance of a neighboring participating group. Preparation of the 1,2-*cis* glycosides is more demanding, because their formation often relies on the anomeric effect. The major strategy for α-glycosylation is the use of a non-participating substituent at C-2. However, there are also other aspects, which can influence 1,2-*cis* glycosylation[86]:

- Leaving group and promoter-assisted glycosylation via a S_N2 mechanism
- Long range participation
- Effect of the participating solvent
- Steric bulkiness at C-6
- Temperature
- Protecting groups in both the donor and the acceptor
- Position of the hydroxyl group in the acceptor

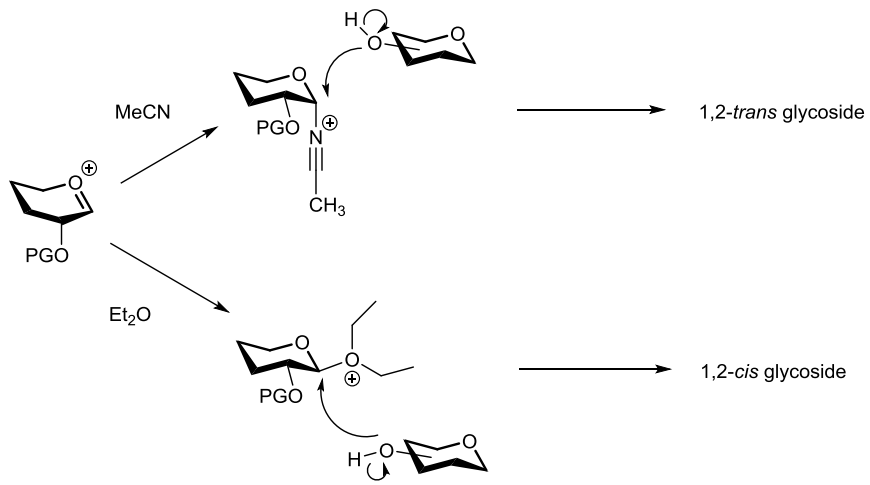
The major requirement for the stereoselective synthesis of 1,2-*cis* glycosides is the presence of a non-participating substituent at C-2. The most frequently used non-participating group is the benzyl ether for neutral sugars. Occasionally, NO_2[87], *O*-methyl[88] or $OCOCCl_3$[89] are also applied. However, the use of a non-participating substituent at C-2 by itself does not guarantee a successful formation of a 1,2-*cis* glycoside.

For the glycosylations that proceed via a S_N2 mechanism with inversion of the anomeric configuration, the leaving group at the anomeric center of the donor is of great importance. In this case, glycosyl donors with 1,2-*cis* orientation form 1,2-*trans* glycosides, which is seen with glycosyl halides and insoluble silver

promoters.[90] On the other hand, 1,2-*trans* glycosyl donors afford 1,2-*cis* glycosides, which is observed with highly reactive β-glucosyl halides,[6] anomeric mannosyl triflates formed *in situ* for the synthesis of β-mannosides[50] or glycosyl thiocyanates.[91]

The substituent at C-2 plays the most important role in the glycosylation, while other substituents are less significant. However, certain substituents at C-6 can influence the stereochemical outcome of a glycosylation. Replacing the 6-*O*-benzyl group of glucose derivatives with an ester or a carbamate results in the preferential formation of α-glucosides.[49,92,93] These observations could be explained by a long range neighboring group assistance of the substituent at C-6. It was also found that steric bulkiness or strong electron-withdrawing properties of the moiety at C-6 promotes α-glycosides. This is made possible by shielding the top face of the ring and favoring the nucleophilic attack from the opposite side.[94, 95, 96, 97, 98] The effect of the substituent at C-6 was found to be insignificant in the D-galacto derivatives,[99] but the effect is strong when the participating substituent is present at C-4.[100, 101] Similar effects were also found for the L-rhamnose and L-fucose[102, 103] derivatives.

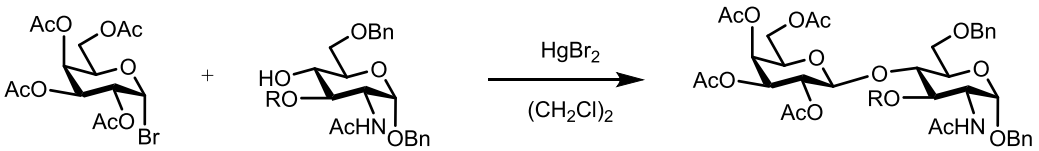
The next important factor influencing the stereoselectivity at the anomeric center is the solvent effect. It has been shown that some solvents in the reaction media have a stereodirecting effect. Polar solvents increase the rate of the β-glycoside formation and non-polar solvents are suitable for forming α-glycosides. Acetonitrile and diethyl ether were found to be the limiting cases for the respective formation of β-D- and α-D-glycosides and the mechanism with these solvents is shown in Scheme 13.



Scheme 13 Solvent effect in the formation of 1,2-*cis* and 1,2-*trans* glycosides.[86]

When the reaction is performed in acetonitrile, the nitrilium cation formed *in situ* exclusively adopts axial orientation and therefore allows stereoselective 1,2-*trans* glycosylation.[104] On the other hand, ether type solvents preferentially form the equatorial intermediate, leading to axial glycosidic bond formation.[105, 106]

Protecting groups influence the electron density on the anomeric carbon, tuning reactivity, but they also effect the electron density of the hydroxyl groups in the sugar, altering their nucleophilicity.[107] Ester electron-withdrawing substituents reduce electron density of the neighboring hydroxyls and therefore lower its nucleophilicity.[107] In the synthesis of a lactosamine derivative, Sinaÿ[108] observed that the protecting group at C3 of the acceptor had a major influence on the glycosylation yield, as shown in Scheme 14.



R = Ac, 5% yield
R = Bn, 87% yield

Scheme 14 Influence of the protecting group on the nucleophilicity of the acceptor and yields of the glycosylation.[108]

The acceptor with an acetyl group at C3 was a very poor nucleophile and the coupling led to the product in a mere 5% yield. Benzyl protection increased the nucleophilicity of the acceptor and the product was now obtained in 87% yield.

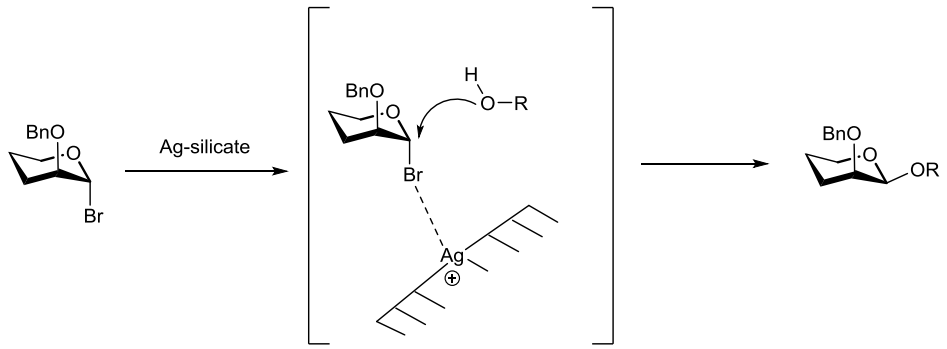
Less reactive hydroxyls can entirely lose their marginal reactivity when surrounded by the deactivating moieties and result in lower glycosylation yields.[109] For example, Hashimoto and co-workers showed glycosylation of the axial 4-OH of galactose that gives exceptional 1,2-*cis* stereoselectivity, exclusively with the use of benzoyl substituents.[110]

Other factors like concentration, temperature and pressure were also studied in terms of glycosylation stereoselectivity. It was found that the higher concentration of the reaction mixture increases the relative rate of the 1,2-*cis* glycoside formation.[106, 111] Different results were observed when the temperature of the reaction was taken into consideration. For example, glycosylations with thioglycosides in the presence of *N*-(phenylseleno)phthalimide and TMSOTf

performed at room temperature led mostly to α-glucosides, while at -45°C the formation of β-glucosides was exclusive.[112] On the contrary, the groups of Schmidt[113] and Kobayashi[114] reported better 1,2-*cis* stereoselectivities achived at lower temperatures. High pressure applied to the glycosylation reactions gave only minimal changes in the stereoselectivity compared to the reaction where normal pressure was applied.[115]

The promoter system and various additives can also often influence the stereochemical outcome of the glycosylation.

The classical Koenigs-Knorr glycosylation with Ag_2CO_3 or AgOTf leads to 1,2-*trans* glycosides. However, glycosylations in the presence of another silver-based heterogeneous promoter Ag-silicate were found to be very efficient for direct β-mannosylations, as shown in Scheme 15.[94, 116]

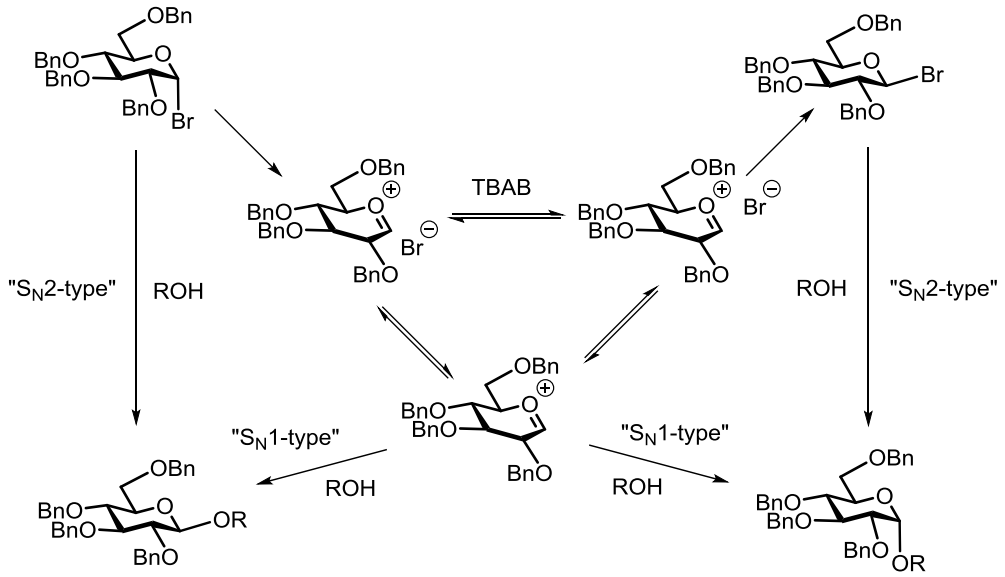


Scheme 15 β-mannosylation by means of Ag(I)-silicate.[116]

The α-side is shielded by the non-soluble promoter, enabling the nucleophile to attack the anomeric center from the other side to afford β-1,2-*cis* glycosides.

Another method for β-mannoside formation was developed by Schuerch[117] and employed silver tosylate as a promoter. This promoter allowed formation of other 1,2-*cis*-linked species like β-L-rhamnopyranosides.[118]

The reactivity of glycosyl halides used in glycosylations is directly connected to the nature of the protecting groups. Traditionally, ether-type substituents are employed, which make the glycosyl donor more reactive towards 1,2-*cis* glycosidic linkages. For the highly reactive donors Lemieux *et al.*[6] developed *in situ* anomerization as shown in Scheme 16, which is promoted by tetraalkylammonium bromide and Hünig's base.[6]



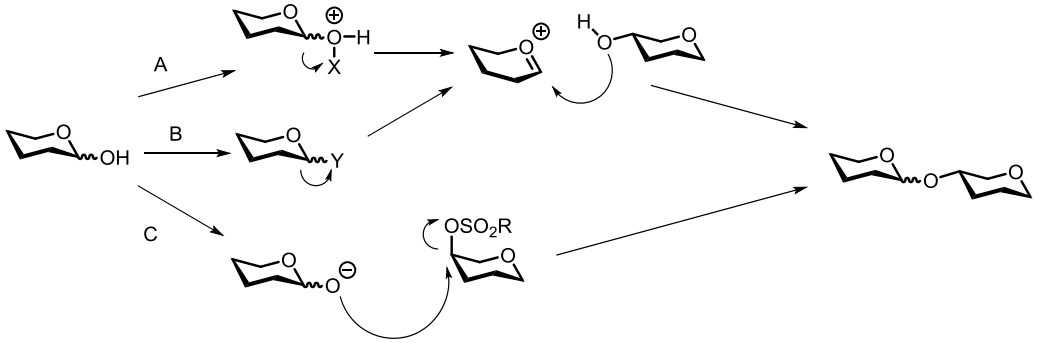
Scheme 16 Lemieux's *in situ* anomerization.[119]

In situ anomerization allows 1,2-*cis* glycosides to be formed as a result of S_N2-type reaction on the anomeric position of a β-glycosyl bromide. Scheme 16 illustrates an *in situ* formation of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl bromide from 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide in the presence of tetrabutylammonium bromide (TBAB). 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl bromide dissociates into the oxocarbenium ion, which forms a tight ion pair with the bromine ion in an α-configuration. Use of TBAB can shift the α-configuration into β-configuration and result in formation of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl bromide. β-glucopyranosyl bromide formed *in situ* is highly reactive and will instantly react with an alcohol acceptor in a S_N2-type fashion and give the 1,2-*cis* product.[119]

Up until now, the *in situ* anomerization procedure in the presence of a tetraalkylammonium halide affords by far better α-selectivity for the derivatives of D-galactose, D-fucose and D-glucose.[120,121] The method has only been demonstrated to be very efficient for the synthesis of complex oligosaccharides if very reactive halides were employed.[121, 120] The work presented by Lemieux and Driguez[122] employed a very reactive fucosyl bromide, which was coupled to a galactosyl acceptor in the presence of tetrabutylammonium bromide, *N*,*N*-diisopropylethylamine and molecular sieves in dichloromethane to afford a 1,2-*cis*-

linked disaccharide. The synthesized disaccharide was converted into a glycosyl acceptor and glycosylated with a galactosyl donor under similar reaction conditions. The trisaccharide achieved with high selectivity proved the synthetic usefulness of Lemieux's newly developed method. In 2007, Kunz and co-workers used *in situ* anomerization conditions in the synthesis of Lewis^X azide by employing lactosamine derivative as an acceptor and fucosyl, arabinosyl and galactosyl bromide as donors in the presence of tetrabutylammonium bromide.[123] Less reactive halide donors like 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl bromide[124] and 2-*O*-(2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-galactopyranosyl)-3,4-di-*O*-benzyl-α-D-xylopyranosyl bromide[125] did not undergo coupling by the *in situ* anomerization protocol, but required $HgBr_2$ and $Hg(CN)_2$ as the promoter.

Glycosyl halides are not the only species that can participate in a 1,2-*cis* glycosylation. There are three general approaches for the synthesis of α-glycosides from 1-hydroxy derivatives, as shown in Scheme 17.

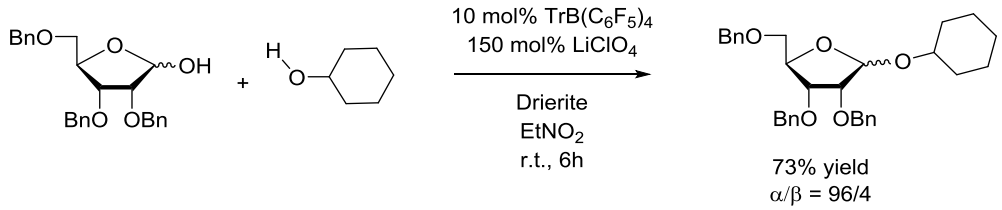


Scheme 17 Ways of using hemiacetals in the 1,2-*cis* glycosylation.

The first two pathways are theoretically similar, where a poor leaving group is converted into a good one by activation with a Lewis or a Brønsted acid (pathway **A**) or via *in situ* conversion into a good leaving group (pathway **B**). The third pathway **C** involves nucleophilic displacement of sulfonated acceptors with an anomeric anion.

The Pathway **A** was studied first by Fischer, who used fully unprotected carbohydrates for the acid-catalyzed reactions to obtain anomeric mixtures of α/β-pyranosides.[126] Subsequent publications, as the work of Posner and Bull,[127] have shown that protected glycosyl donors with an anomeric hydroxyl group will undergo self-condensation under these conditions to afford 1,1'-disaccharides. For that reason, the method can be only applied in the glycosylation of highly reactive

acceptors like primary aliphatic alcohols. Excellent 1,2-*cis* stereoselectivity in the approach **A** was discovered, when lithium salts were used as an additive. Adding $LiClO_4$ to the trityl cation-catalyzed glycosylations gave mainly the α-linked product, whereas in the absence of the lithium salts, the β-linked products were predominantly formed.[128] In Scheme 18 an example of a glycosylation with the lithium salt is shown.



Scheme 18 Example of glycosylation with lithium salt.

Complexation of the lithium cation with O-4 and O-5 of ribofuranose derivatives, results in shielding the top face of the molecule and preventing the formation of a 1,2-*trans* glycoside. In Figure 5 the possible intermediate of this reaction is presented.

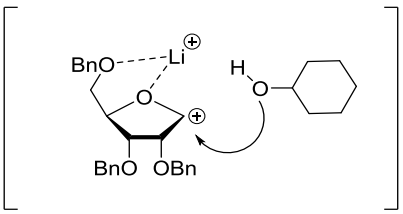
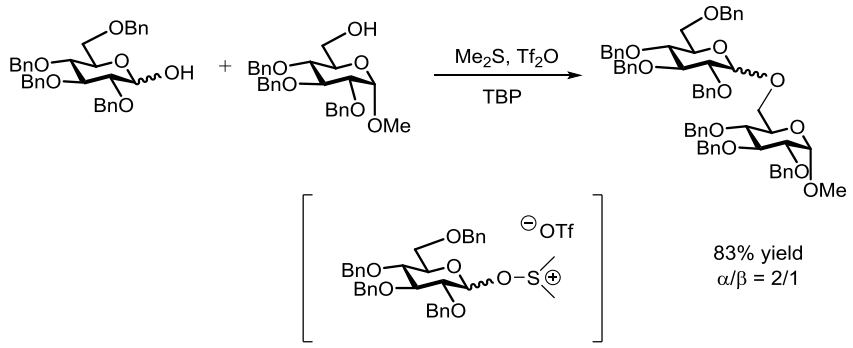


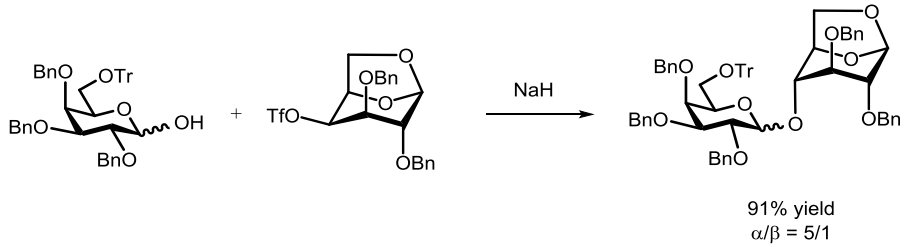
Figure 5 Possible intermediate formed during 1,2-*cis* glycosylation with lithium salts.[128]

The pathway **B** combines anomeric derivatization, activation and glycosylation in one synthetic step. The hemiacetal is usually converted into other more effective leaving groups like halide, sulfonyl or silyl derivative *in situ*. Significant effort was put into developing new activating systems. One of the most efficient synthetic methods involves the activation of a hemiacetal via in situ generation of an oxosulfonium ion intermediate in the presence of dimethyl sulfide, triflic anhydride and 2,4,6-tri-*t*-butylpyridine (TBP), as shown in Scheme 19.[129]



Scheme 19 Example of 1,2-*cis* glycosylation with hemiacetals with formation of oxosulfonium ion intermediate.[129]

The last pathway **C** describes nucleophilic displacement of the primary and secondary triflates with an anomeric anion that is obtained *in situ* by treatment with NaH. These glycosylations typically go on with retention of the anomeric configuration.[130] The displacement of the secondary triflates leads to the inversion of the configuration of the glycosyl acceptor. Consequently, NaH-promoted glycosylation of the triflate of 1,6-anhydro-2,3-di-*O*-benzylgalactose acceptor with a 1-hydroxy derivative of galactose afforded a disaccharide as a mixture of α:β anomers in a 5:1 ratio, as it is shown in Scheme 20.[131]

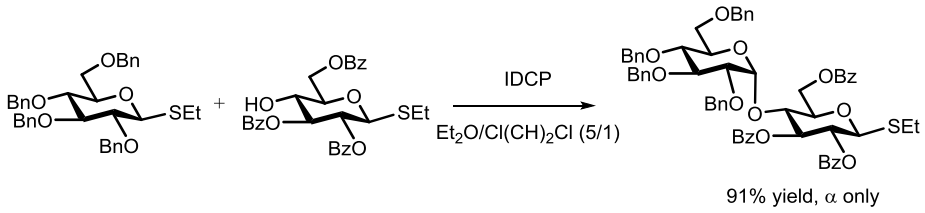


Scheme 20 NaH-promoted glycosylation of a triflate acceptor with a 1-hydroxy derivative of galactose.

As mentioned above, 1,2-*cis*-linked glycosylations with hemiacetals as donors might be troublesome in terms of stereoselectivity. High yields and better stereoselectivity can be provided when acetimidates, especially *N*-methyl are employed as donors.[28] The synthesis of acetimidates has been described in **2.2.2** and consequently only their use in 1,2-*cis* glycosylations will be mentioned. The synthesis of α-glycosides is typically initiated from β-trichloroacetimidates and indeed, the glycosylation of the primary hydroxyl group with a β-galactosyl imidate gave the corresponding disaccharide as a 8:1 mixture of α:β-anomers, when

TMSOTf was used as the promoter.[132] When highly reactive donors like the fully benzylated fucosyl trichloroacetimidate was used, some difficulties were encountered. The problem was addressed by the introduction of the 'inverse procedure'.[133] The concept of the inverse procedure assumes that the highly reactive donors might decompose in the presence of a promoter before being able to react with a glycosyl acceptor. In the above-mentioned case with the fucosyl donor, adding the donor to the mixture of the glycosyl acceptor and the promoter increases the yield of the α-product from 43% achieved by the regular procedure, to 79%. As an example, the trichloroacetimidate method has been successfully used for a number of glycosylation steps during the target synthesis of a tumor-associated glycosphingolipid monosialylgalactosylgloboside.[134]

Another important class of donors are thioglycosides. Usual promoters like DMTST, NIS/TfOH or NIS/TMSOTf proved to be less effective in performing the 1,2-*cis* glycosylations in a stereocontrolled manner and only a few successfully accomplished 1,2-*cis* glycosylations have been reported.[135, 136, 137, 107] Typically, the promoter of choice for the stereoselective 1,2-*cis* glycosylation with thioglycosides is iodine dicollidine perchlorate (IDCP).[106, 138] An exceptional yield and stereoselectivity was observed when secondary hydroxyl groups were glycosylated at room temperature in 1,2-dichloroethane/diethyl ether, as shown in Scheme 21.[14]



Scheme 21 Example of glycosylation with IDCP used as the promoter.[14]

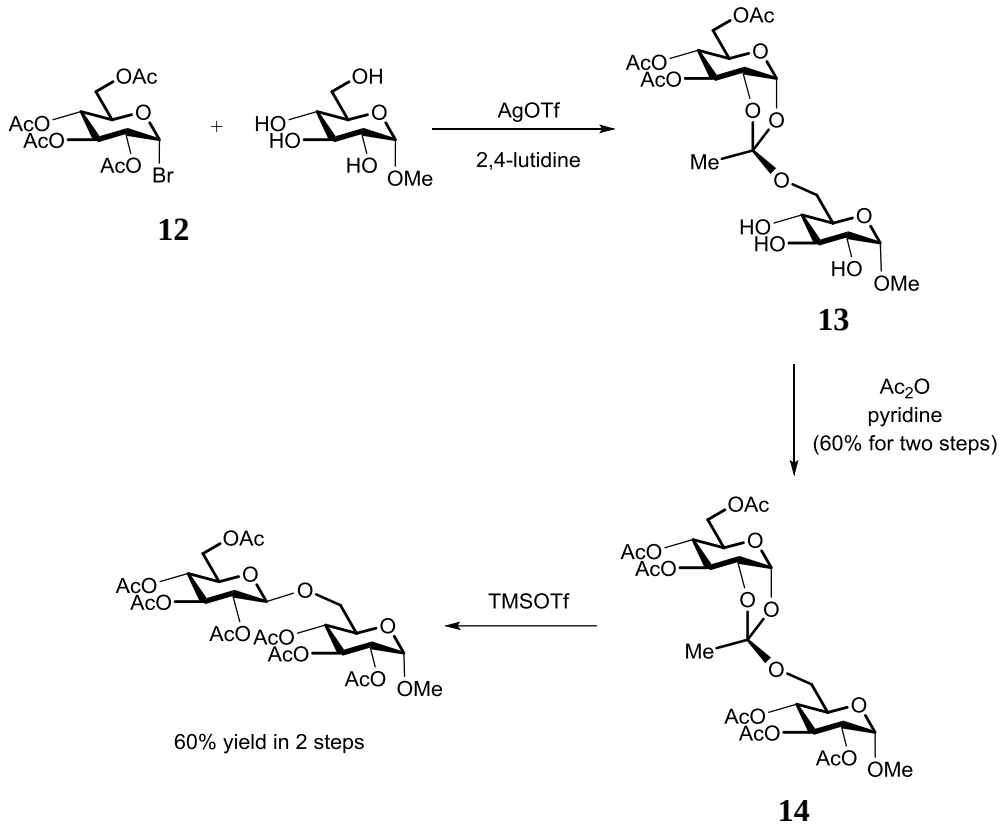
The same conditions were applied to the acceptor with a free primary hydroxyl group. In this case, the corresponding disaccharide was formed as an anomeric mixture (α/β=2.5/1) in a high 94% yield.[14]

Thioglycosides are some of the most capable donors used in oligosaccharide synthesis to date. However, developing new catalytic systems for the 1,2-*cis* glycosylation is still in demand.

2.4 Glycosylation with unprotected or partially protected carbohydrates

The use of unprotected or partially protected carbohydrates in the glycosylation would be a great facilitation in the synthesis of oligosaccharides. Studies with unprotected or lightly protected mannose,[139] glucose,[140] rhamnose[141] and glucosamine[142] acceptors have been reported.

The work of Wang and Kong[140] describes the preparation of oligosaccharide orthoesters using unprotected/partially protected glucosides as acceptors and glucosyl bromides as the donors. The reaction is shown in Scheme 22.

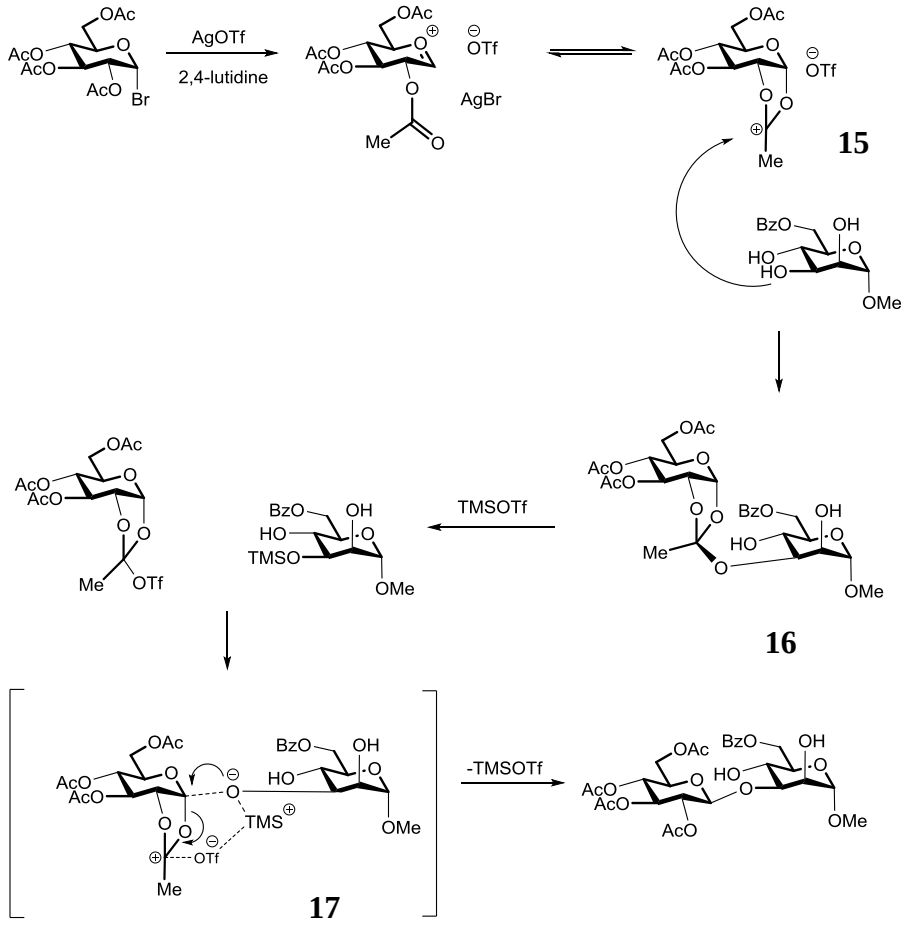


Scheme 22 Example of glycosylation via orthoester intermediates.[140]

Acetobromoglucose **12** was coupled to the unprotected methyl glucopyranoside by means of AgOTf in the presence of 2,4-lutidine. This led to the formation of the 6-

linked orthoester **13**. Subsequent acetylation of **13** gave **14** and rearrangement of the **14** with catalytic amount of TMSOTf afforded the β-(1→6)-linked disaccharide in 60% yield.

After the series of experiments on different donors and acceptors, there was a clear indication that in the orthoester formation and rearrangement, the reactivity of the primary hydroxyl group in glucose and mannose acceptors is higher than the reactivity of secondary groups. Moreover, the reactivity of 3-OH is higher than the reactivity of 2-OH and 4-OH.[143] A possible mechanism of the reaction was presented as shown in Scheme 23. The orthoester was formed by coupling the bridging dioxolenium ion **15** with the 3-OH group of the mannosyl acceptor. The presence of the base decreased the coupling reaction rate, leading to the formation of **15** and then the orthoester **16**.

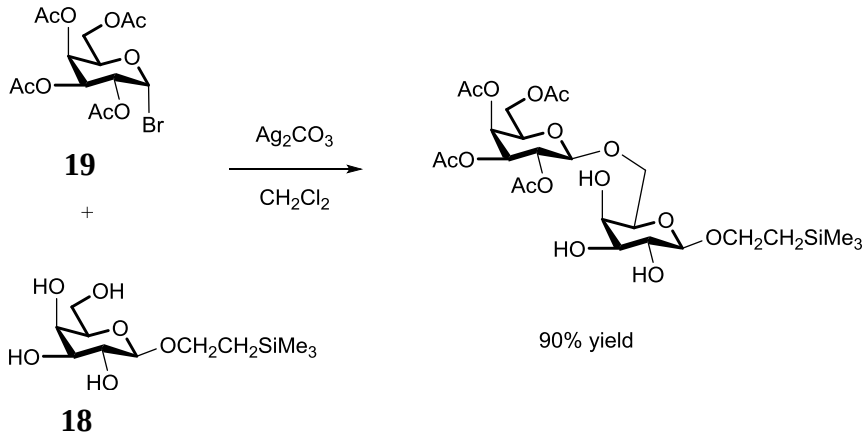


Scheme 23 Proposed mechanism of the glycosylation via orthoester intermediate.[139]

The orthoester rearrangement was supposed to be an intramolecular reaction and after TMSOTf addition via six-membered ring geometry intermediate **17**, rearrangement occurs to form the disaccharide.[139]

The example above shows regioselective glycosylation with unprotected glucosyl and mannosyl acceptors via an orthoesther formation.

In 1995, Kartha *et al.*[144] used a fully unprotected galactopyranoside as an acceptor in the direct regio- and stereoselective synthesis of β-(1→6)-linked oligosaccharides, as shown in Scheme 24.



Scheme 24 Example of glycosylation with fully unprotected galactopyranoside acceptor.

2-(Trimethylsilyl)ethyl β-D-galactoside (**18**) in dichloromethane was treated with acetobromogalactose **19** in the presence of silver carbonate and molecular sieves to give the β-(1→6)-linked product in 90% yield. Only minor amounts of the β-(1→4)-linked disaccharide were isolated as by-product in the reaction. Changing the solvent to acetonitrile or toluene did not improve the glycosylation yields. Substituting silver carbonate by a hindered base such as collidine did not yield any disaccharide product. The same acceptor could be selectively benzoylated at the 6 position and give β-(2→3)-linked disaccharide in 52% yield, while using DMTST as a promoter and a sialic acid thioglycoside as the donor.[145]

An interesting study using a base-promoted glycosylation comes from Thiem and co-workers.[146, 147, 148] The study describes glycosylation by formation of oxyanions using partially protected acceptors. Deprotonation of acceptor hydroxyl groups giving oxyanions should lead to direct and selective glycosylation on partially protected and unprotected sugars and result in shorter routes to oligosaccharides, essentially decreasing the number of steps in the total process. Glycosylation with fully unprotected acceptors failed, mostly due to solubility reasons but studies with the monoprotected glycosyl acceptors have also been done in the course of the work and are shown in Figure 6.

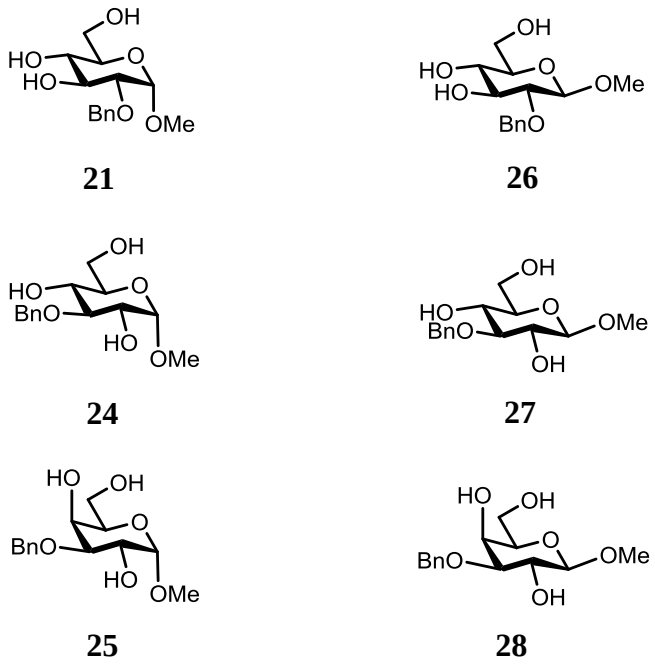
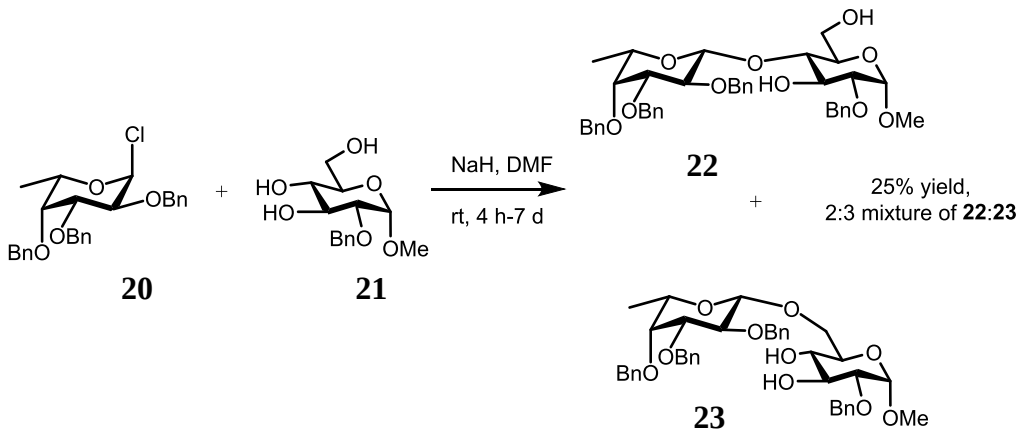


Figure 6 Monoprotected glycosyl acceptors investigated in the regioselective glycosylation.

All acceptors underwent glycosylation with a benzylated fucosyl donor **20**, as shown in Scheme 25.

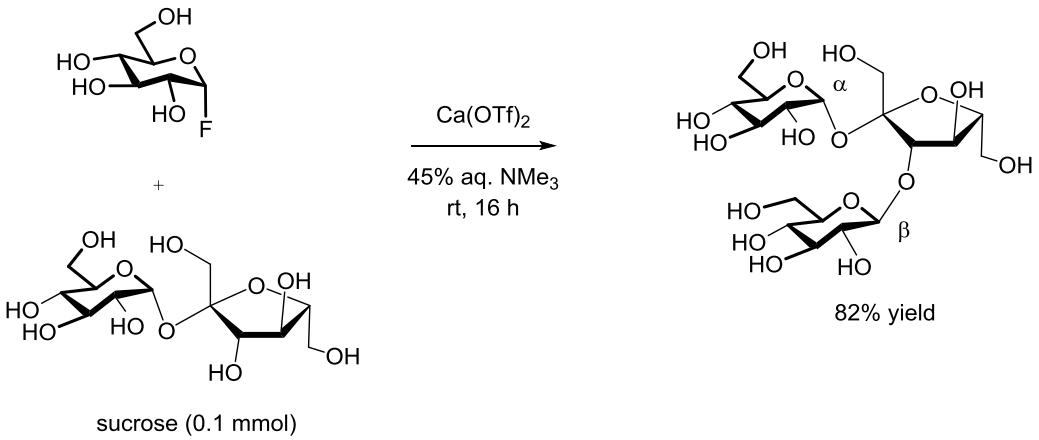


Scheme 25 Example of glycosylation with benzylated fucosyl donor.[148]

Methyl 2-*O*-benzyl-α-D-glucopyranoside (**21**) gave a 2:3 mixture of the β-(1→4)-linked **22** and the β-(1→6)-linked disaccharide **23** in the glycosylation and the

reaction gave a total yield of 25%. Methyl 3-*O*-benzyl-α-D-glucopyranoside (**24**) led to the β-(1→2)-linked and the β-(1→6)-linked disaccharide in a 1:7 ratio and with a combined yield of 48%. Methyl 3-*O*-benzyl-α-D-galactopyranoside (**25**) gave only the β-(1→6)-linked disaccharide in a 33% yield. From methyl β-glycoside acceptors, only **26** underwent the glycosylation and led to the β-(1→6)-linked disaccharide in 30% yield. Acceptors **27** and **28** did not react with the fucopyranosyl chloride at all. The anomeric configuration in the acceptor has a profound effect on the glycosylation and results in lower oxyanion reactivity for methyl β-glycopyranosides. After extensive studies, Thiem and co-workers proposed the reactivity arrangement for isolated hydroxyl functions in methyl α-D-glucopyranosides as follows: 2-OH>4-OH>6-OH>3-OH. However, the above-mentioned results leave significant room for improvement in terms of yields and regioselectivity.

A very recent study describing glycosylation of unprotected glucosyl fluoride donor with unprotected disaccharides used as acceptors was published by Miller and co-workers.[149] The model reaction is shown in Scheme 26.



Scheme 26 The 3'-glycosylation using $Ca(OTf)_2$.[149]

The trisaccharide was formed under aqueous conditions in the presence of Ca^{2+} salts that was found to be the only effective salts at promoting the glycosylation over hydrolysis. Other di-, tri- and tetrasaccharrides with a sucrose-like moiety have also been employed as acceptors in the glycosylation under the optimized conditions and the results showed very good yields of exclusively the 3'-glycosylated products.

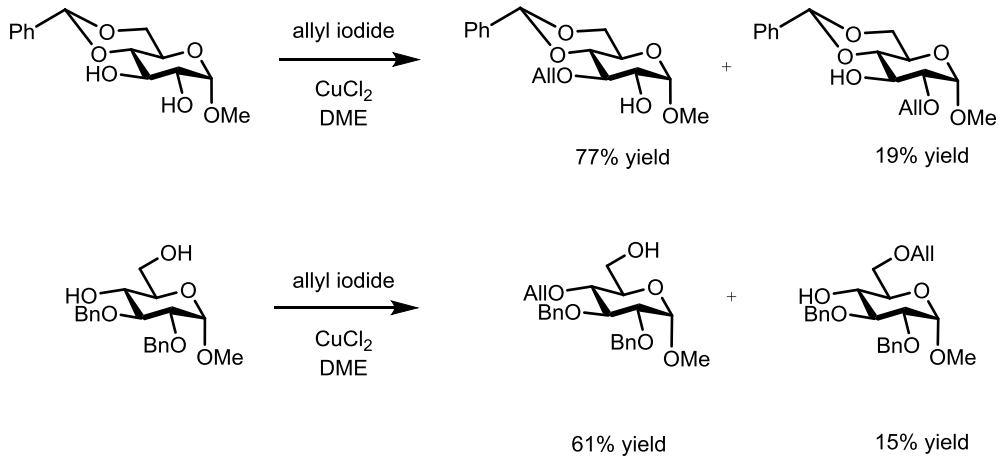
2.5 Metal-mediated alkylations, acylations and glycosylations

Contemporary chemical synthesis is a rather time consuming process for assembling oligosaccharides and more rapid approaches are in high demand. A particular daunting task is the need for special protecting groups to selectively block hydroxy groups that are not involved in the coupling. This leads to a significant number of additional steps for manipulating these groups every single time a target oligosaccharide has to be prepared. Therefore, it would be highly desirable to couple monosaccharides without the use of protecting groups.

Enhancing the differences in the reactivity between the hydroxyl groups in carbohydrates could be achieved either by activating the target hydroxyl group or by deactivating the remaining hydroxyl groups. Examples of metals, which can be exploited to mediate alkylations, esterifications and glycosylations of unprotected sugars have been reported.[150, 151, 152]

One of the first reported regioselective acylation and alkylation reactions with the use of transition metals comes from Schuerch *et al*.[152] In the preliminary studies they reported the application of copper (II) salts to the regioselective alkylation (with benzyl, methyl, allyl) halides of carbohydrate diols.

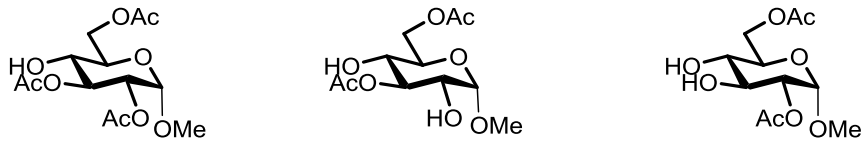
During further investigation, Schuerch and co-workers[153] employed only benzyl and allyl halides in the regioselective alkylation of methyl 4,6-*O*-benzylidene-α-D-glycopyranosides and methyl 2,3-di-*O*-benzyl-α-D-gluco- and galactopyranosides. The best results have been obtained, when alkyl iodides were used. In all cases, only monosubstituted products were isolated and no disubstituted product was observed, as shown in Scheme 27.



Scheme 27 Example of regioselective allylation in the presence of copper (II) salt.[153]

In the same study, copper(II) and mercury(II) salts have been used in an acylation reaction. For comparison, the standard procedure with pyridine and acetic anhydride was also used. Reactions with metal chelates and acetylating agents were very fast and mercury complexes led to completion within 10 minutes (1 hour for copper chelates and 48 hours for reactions in pyridine). In general, metal chelates gave monoacetylated compounds as the major product, but a significant amount of disubstituted product was also formed.[153]

In 1990 Hanessian and Kagotani[154] published a method for the preparation of partially acetylated carbohydrates in the presence of zinc chloride. Methyl α-D-glucopyranoside was dissolved in a mixture of dimethylformamide and pyridine in the presence of divalent metal salts. A control experiment without the metal ions was also performed. In the absence of metal ions, a very random pattern of acetylation was noticed. However, two main products were observed, namely the triacetate **29** and the diacetate **30**, as shown in Figure 7. When zinc chloride was used, 2,6-diacetate derivative **31** was isolated in a 65% yield, also shown in Figure 7.

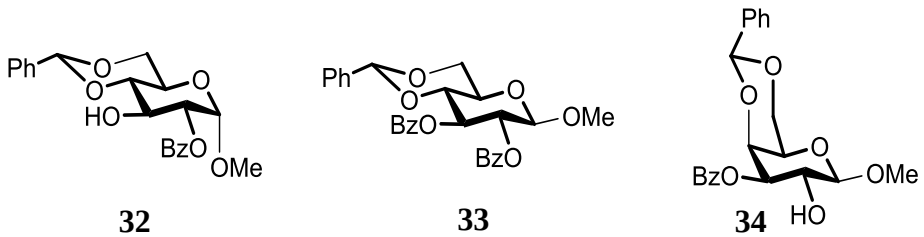


29 **30** **31**

Figure 7 Acetylated monosaccharides formed during the investigation of regioselective acetylation.

Other metal salts were investigated in the selective acetylation and it was found that mercuric acetate was less effective, while magnesium and calcium chloride favored the formation of mixtures of monoacetates, among other products. The same method was applied to methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, which led to a favored acetylation of the 2-hydroxyl group. A significant amount of the diacetate was also formed. In the absence of zinc chloride, equal amounts of the two monoacetates were formed.[154]

Another attempt to develop new strategies for the regioselective protection of carbohydrates was made by Demchenko *et al.*[155] The studies on metal chelates and their effect on the regioselective protection of vicinal 2,3-diols of monosaccharides were reported and products of the benzoylation are shown in Figure 8. Nickel(II), platinum(II) and zinc(II) salts have been investigated in the monoalkylation and monoacylation reactions. Benzylidene protected α-D-glucopyranoside was selected for the initial studies. Benzoylation with benzoyl chloride in the presence of pyridine or sodium hydride and without the metal salt proceeded with poor selectivity. When the metal salts were used in the reaction, namely nickel chloride, platinum chloride and zinc chloride, only the 2-*O*-substituted product **32** was formed.

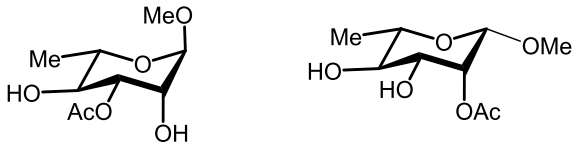


32 **33** **34**

Figure 8 Products of regioselective benzoylation with nickel chloride. [155]

The concept was applied to other monosaccharides but it did not work well for the β-gluco series, where dibenzoylated product **33** was obtained, possibly because all substituents are equatorially oriented. Many factors can influence the stability of the complex, such as reaction conditions, geometry around the metal center or ionic radius of the metal ion. The concept was tested on the derivative from the β-galactose series and the metal-assisted benzoylation proceeded with high regioselectivity to give 3-*O*-substituted product **34**. The best results were obtained with nickel chloride, however, zinc and platinum chlorides also showed high regioselectivity. [155]

Recently, Evtushenko published his work on regioselective acetylation[151] and benzoylation[156] with molybdenum compounds. The results of this work are shown in Figure 9. $MoCl_5$ was used as a catalyst in the regioselective acetylation of methyl glycosides. The use of the metal complex led to regioselective formation of the 3-acetate of methyl α-L-rhamnopyranoside **35**. Under the same conditions, methyl β-L-rhamnopyranoside formed the 2-acetate **36**.



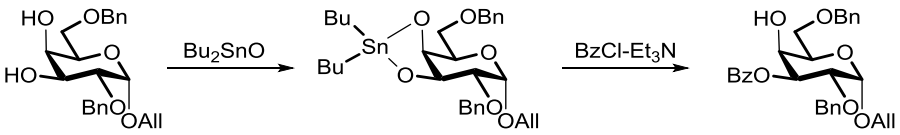
35 **36**

Figure 9 Products of regioselective acetylation with molybdenum salt.[151]

The acetylation of methyl pyranosides of α-and β-L-arabinose, α-D-fucose, β-D-ribose and α-D-lyxose led to the 3-acetate as the main product.[151] On the contrary, methyl β-D-xylopyranoside with no cis-vicinal hydroxyl groups led to a mixture of acetates, mostly from acetylation in the 2- and 4-position. Other metal complexes were also studied in the regioselective acetylation, such as $CeCl_3$, YCl_3, $Cu(CF_3COO)_2$ and $Hg(CF_3COO)_2$.[151] However, they all led to the mixture of 2- and 3-acetates, possibly, because these transition-metals form intermediate bidentate complexes with *cis*-vicinal hydroxyl groups of methyl α-L-rhamnopyranoside.

This approach was extended with benzoylation of carbohydrates by benzoic anhydride. It was found, however, that $MoCl_5$ was not active in this reaction. Another molybdenum complex, $MoO_2(acac)_2$, was investigated and it led to regioselective benzoylation at 3-OH in almost all tested compounds. Only in methyl β-L-rhamnopyranoside did the benzoylation afford the 2-benzoate predominantly.[156]

So far, the most investigated metal in the regioselective acylation and alkylation is tin.[157] In 1976, Nashed and Anderson[158] found that in the *cis*-vicinal diol system a five-membered stannylene ring is formed between the axial-equatorial pair and that the reactivity of the equatorial hydroxyl is enhanced more than the axial one. The species are shown in Scheme 28.



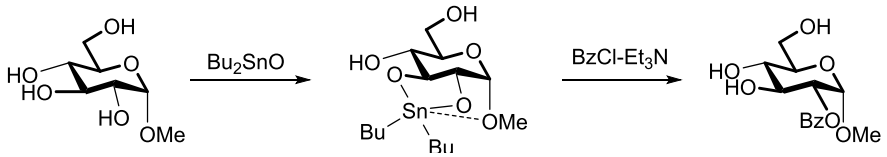
37 **38**

81% yield

Scheme 28 Example of benzoylation with dibutyltin oxide.[158]

In this way, they selectively obtained benzoylation at the 3 position of galactoside **37** to afford **38** by means of benzoyl chloride and triethylamine, after treatment with dibutyltin oxide in methanol.

The same tin compound was used by Munavu *et al.*[159] in the benzoylation of methyl α-D-glucopyranoside. This reaction led to the formation of the 2-benzoate **39**, as shown in Scheme 29.



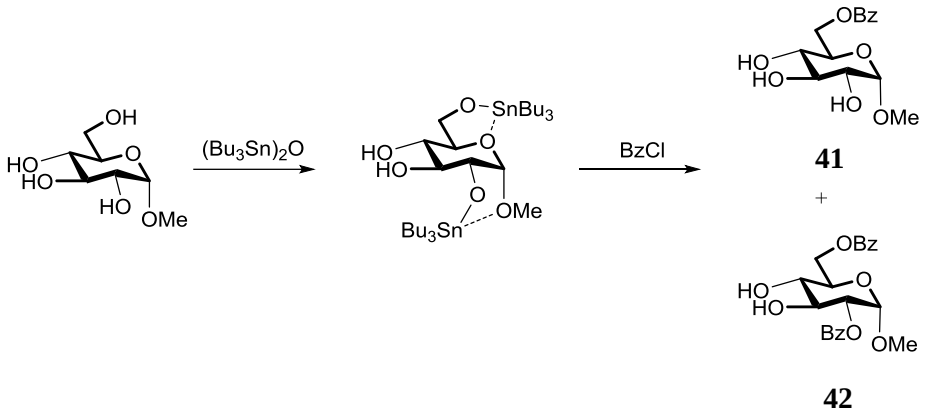
40 **39**

71% yield

Scheme 29 Example of benzoylation with dibutyltin oxide on unprotected glucoside.[159]

In this case, it was suggested that the formation of the five-membered stannylene ring **40** between the two equatorial hydroxyls would be favored by coordination of the neighboring oxygen atom, which has an axial orientation as compared to the tin atom.

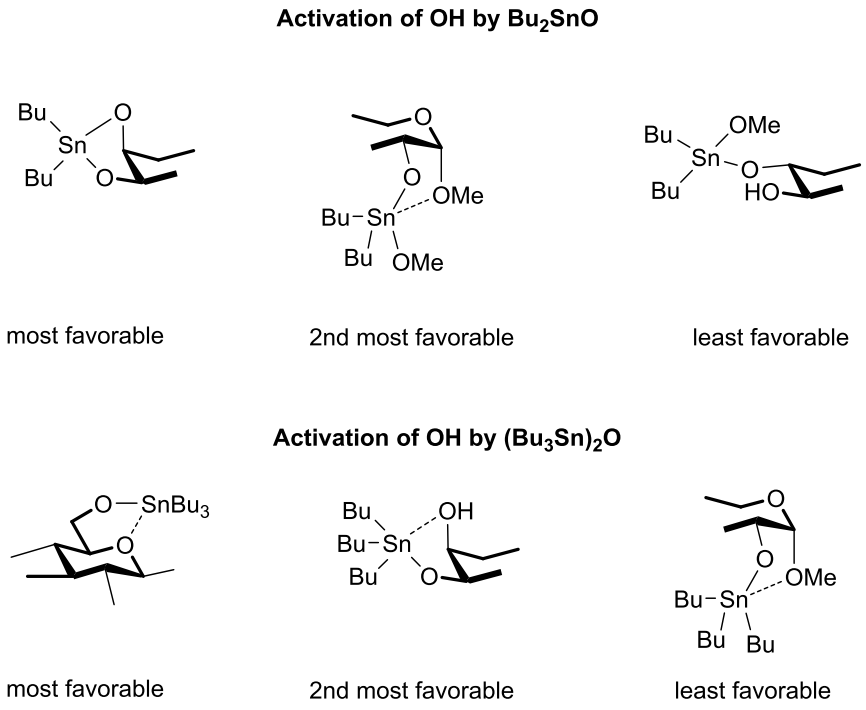
Later studies on the organotin compounds include the use of bis(tributyl)tin oxide for the regioselective acylation of some pyranosides. The work of Ogawa and co-workers[160] is shown in Scheme 30.



Scheme 30 Regioselective benzoylation by means of bis(tributyl)tin oxide.

The formation of the trialkyltin ether and its stabilization by coordination of a neighboring oxygen atom was suggested. As a result, 6-benzoate **41** was formed in a 73% yield, while a significant amount of the 2,6-benzoate **42** was also present in the reaction mixture.

Tsuda and co-workers[161] also made extensive studies on the use of bis(tributyl)tin oxide and dibutyltin oxide and proposed mechanisms for enhancement of the reactivity of the hydroxyl groups, depending on the stereochemical arrangement of these groups. Their model is shown in Scheme 31. In the method with dibutyltin oxide the formation of the 5-membered stannylene ring is most favorable and stable at the *cis*-vicinal diol. Methyl β-L-arabinopyranoside, phenyl α-L-arabinopyranoside, methyl α-D-galactopyranoside, methyl α-D-galactopyranoside and methyl α-D-mannopyranoside are examples of sugars, where the equatorial hydroxyl is activated without exception. The second most favorable option is when *cis*-vicinal diols are not available for stannylene ring formation and the tin acetal is stabilized by coordinating with a neighboring oxygen atom of the *cis* arrangement, like in methyl α-D-glucopyranoside and methyl α-D-xylopyranoside.[161]



Scheme 31 Comparison of hydroxyl activation by means of dibutyltin oxide and bis(tributyl)tin oxide.[161]

When the above described sequences (covalent and coordination) are not available for the ring formation, dibutyltin oxide only enhances the reactivity of the most reactive hydroxyl group.[161]

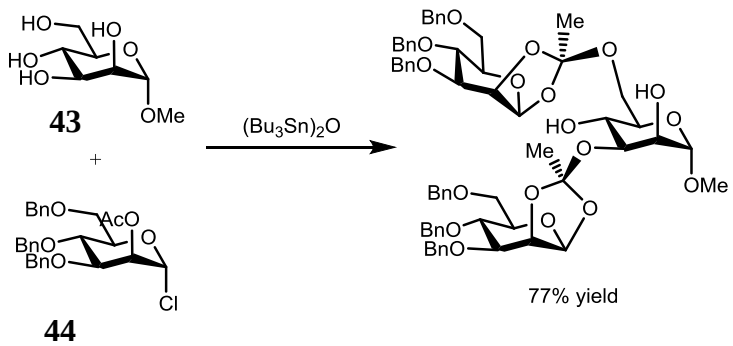
Bis(tributyl)tin oxide enhances first the reactivity of the most reactive hydroxyl group by forming a tin ether that is stabilized by coordination with the neighboring group atom in the *cis* fashion. Then the reaction proceeds similarly to the reaction with dibutyltin oxide.[161]

The application of dibutyltin oxide and bis(tributyl)tin oxide gives the possibility to introduce an acyl group regioselectively in the sugar. The main advantage of the dibutyltin oxide procedure is that the reagent changes the order of the reactivity of the hydroxyl groups and activates a specific secondary OH group in a *cis*-vicinal diol system even when a more reactive primary hydroxyl group is present.[161]

2.5.1 Tin-mediated glycosylations

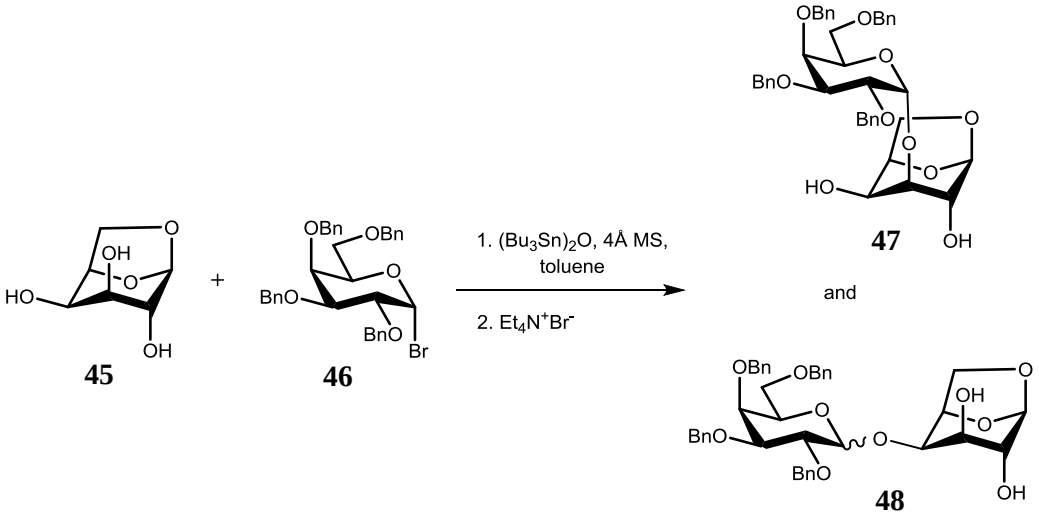
Over the years, new methods for the regioselective glycosylations have been continuously investigated. As described in the previous paragraphs significant attention was directed to glycosylation with fully unprotected or partially protected carbohydrates both with standard protecting groups and with the use of metals. Glycosylations with fully unprotected acceptors often deal with solubility problems and to prepare partially protected acceptors protecting/deprotecting steps have to be used, which makes the process longer and less effective. In the metal mediated glycosylations protecting/deprotecting steps could be avoided and as a result, suitable metal complexes for making selective alkylations, acylations and finally glycosylations have been intensely investigated. After years of study, tin compounds were found to be the most successful in the selective alkylation and esterification of hydroxyl groups in sugars. Therefore, it is not surprising that the next step was to test their abilities in the regioselective glycosylation.

The first examples of using tin compounds in the glycosylation come from the late seventies and were published by Ogawa and co-workers.[162] The regiocontrolled activation of the hydroxyl groups in methyl α-D-mannopyranoside (**43**) through tributylstannylation was described. As shown in Scheme 32, treatment of **43** with bis(tributyltin)oxide in refluxing toluene and then reaction with 2-*O*-acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl chloride (**44**) gave the orthoester at the 6-*O* and 3-*O* positions in a 77% yield.



Scheme 32 Example of glycosylation of unprotected mannosyl acceptor by means of bis(tributyl)tin oxide.[162]

In the late eighties another example of tributyltin ether-mediated glycosylations was shown by Martin-Lomas *et al.*[163] The reactions were catalyzed by tetraethylammonium halides and the regioselectivity studies were carried out under common conditions with toluene or dichloromethane as the solvent. In the example in Scheme 33, 1,6-anhydro-β-D-galactopyranose (**45**) was activated by bis(tributyltin)oxide and then subjected to glycosylation with tetra-*O*-benzyl-α-D-galactopyranosyl bromide (**46**) in the presence of tetraalkylammonium bromide.

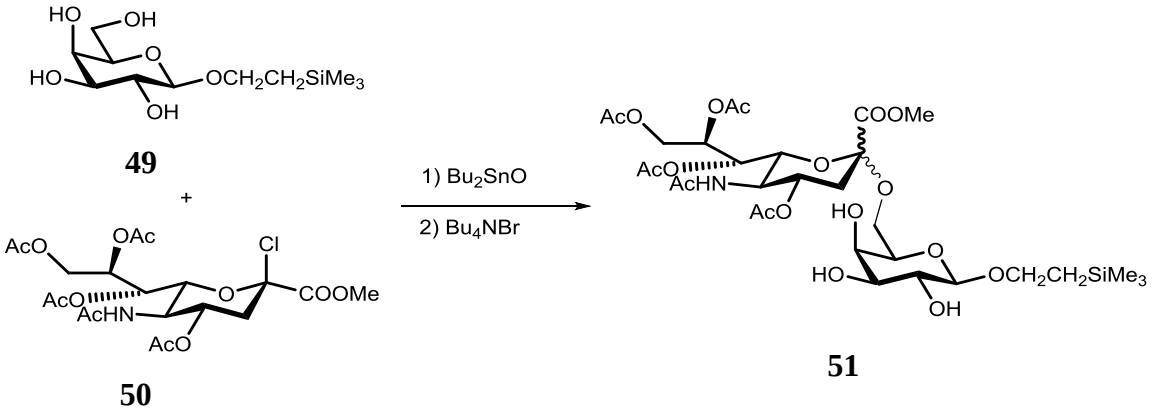


Scheme 33 Glycosylation wit bis(tributyl)tin oxide and tetraetylammonium bromide.[163]

The reaction yielded a mixture containing the α-(1→3)-linked disaccharide **47** and the α/β(1→4)-linked disaccharides **48**. Changes in the solvent and the reaction temperature affected the ratio between the different regio- and stereoisomers. In fact, when the reaction was performed in toluene at 60 °C, 14% of **47** and 79% of **48** in a 1:4 α/β mixture of the disaccharides were obtained. When the reaction was carried out in dichloromethane at room temperature, 30% of disaccharide **47** and 50% of **48** in a 1:2.5 α/β mixture were formed.[163]

At the same time, Murase and co-workers[164] reported the tin-mediated regioselective glycosylation with a galactopyranosyl acceptor containing four unprotected hydroxyl groups, as shown in Scheme 34. This time, 2-(trimethylsilyl)ethyl β-D-galactopyranoside (**49**) was treated with dibutyltin oxide. It then reacted with peracetylated neuraminic acid glycosyl chloride donor **50** in the

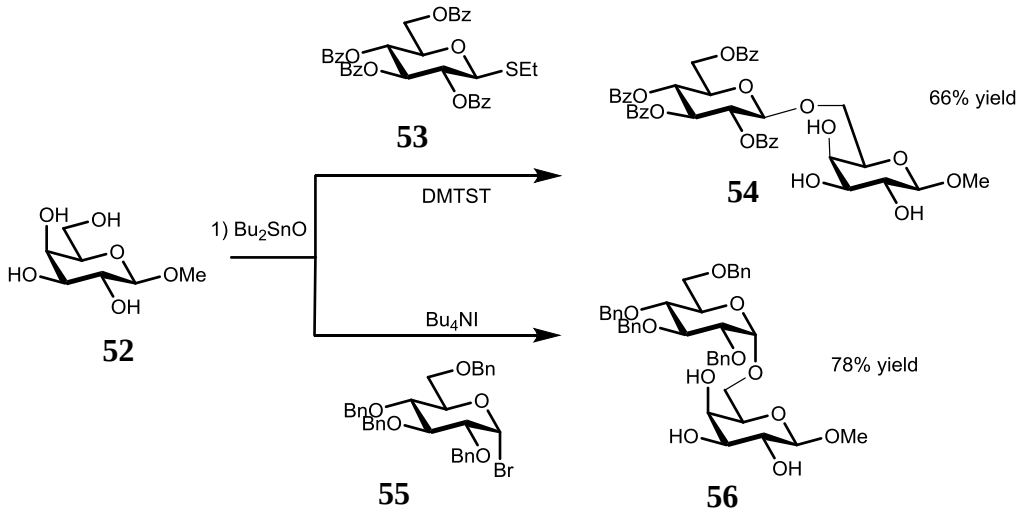
presence of tetrabutylammonium bromide to give exclusively the α and the β-(1→6)-linked disaccharides (**51** α/β) in 36% and 23% yields, respectively.



Scheme 34 Dibutyltin oxide mediated glycosylation.[164]

Previous reports on the reaction of the 3,4-*cis*-diol structure in unprotected galactopyranose derivatives have shown the formation of 3-*O*-substituted derivatives[165] and the observed 1→6 regioselectivity in Scheme 34 was surprising and could not be explained by the authors.

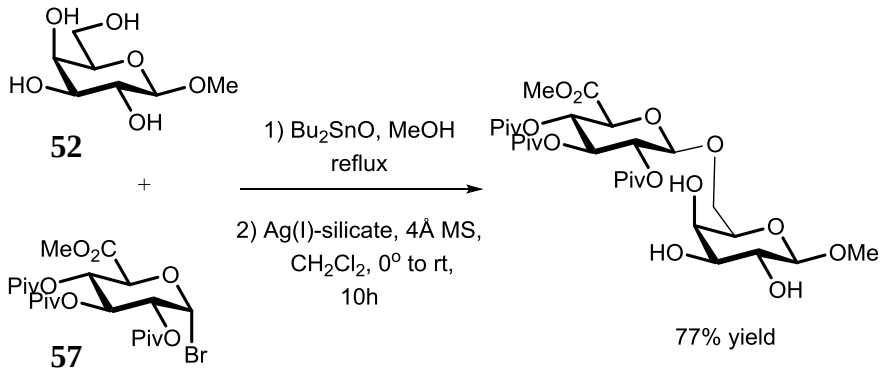
The same selectivity, however, was reported later by Oscarson and co-workers.[166] Methyl β-D-galactopyranside (**52**) was coupled with different donors to give 1→6 glycosylation products as shown in Scheme 35.



Scheme 35 1,6-Linked products of glycosylation with methyl β-D-galactopyranside.[166]

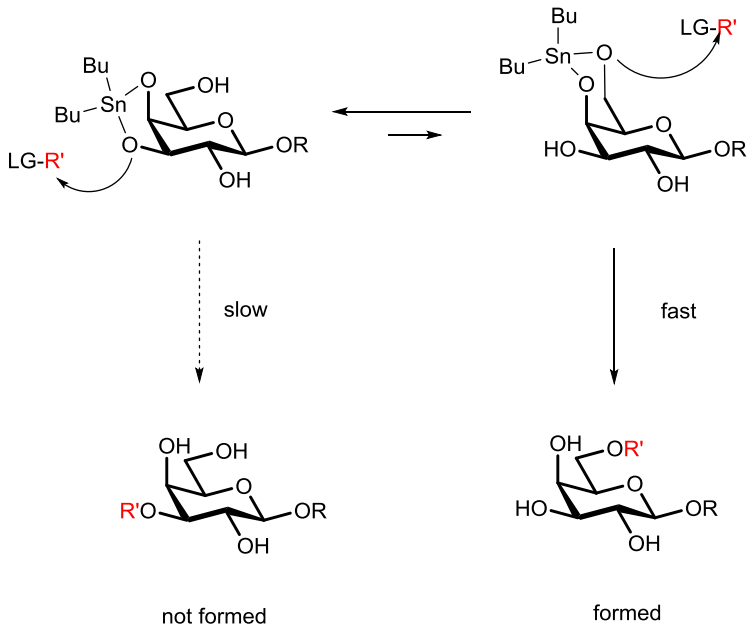
Glycosylation with galactose derivative **52** and benzoylated thioglucoside **53** was performed by treatment with dibutyltin oxide and activation with DMTST to give the β(1→6)-linked product **54** as the only product in good yields. It was also possible to use glucopyranosyl bromide **55** under Lemieux conditions to form the α(1→6)-linked product **56** in a 78% yield.

The use of dibutyltin oxide in glycosylations with fully unprotected galactosides and rhamnosides has also been studied by Kaji and co-workers.[167] In Scheme 36 the coupling of the stannylene derivative of galactopyranoside **52** with glucuronyl bromide donor **57** is shown. As a promoter in the reaction, Ag(I)-silica alumina was used and the β(1→6)-linked product was obtained in a 77% yield.



Scheme 36 Regioselective glycosylation with dibutyltin oxide and Ag(I)-silicate.[167]

Additionally, the regioselective glycosylation between the stannylene acetal of methyl α-L-rhamnopyranoside and glucuronyl bromide was performed. The resulting product was a β(1→3)-linked disaccharide obtained in a moderate yield of 46%. The regioselectivity observed for the stannylene-mediated glycosylations could depend on the reactivity of the different stannylated structures that are present in equilibrium.[167] The hypothesis is presented in Scheme 37 and constitutes an example of the Curtin-Hammett principle. Assuming that the 3,4- and the 4,6-stannylene acetals are rapidly equilibrating, the product ratio will only depend on the ease of the subsequent glycosylation reaction and not on the ratio between the two stannylene acetals.

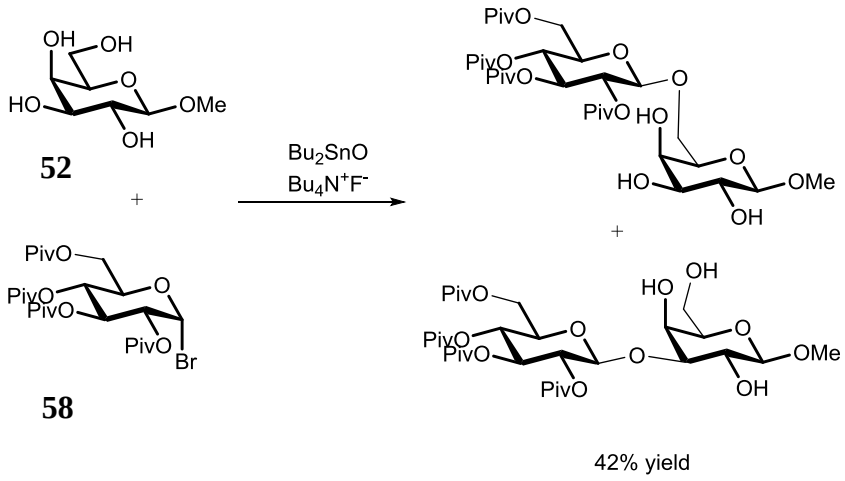


Scheme 37 Reactivity of different stannylenes.

Studies made by Tsuda and co-workers have shown that the enhancement of the reactivity of hydroxyl groups in tin-mediated reactions depends mainly on the stereochemical arrangement of the hydroxyl groups.[161, 168] As described above, when the alkylations and acylations were presented, in the case of galacto- and mannopyranosides the stannylene acetal formation is most favorable at the *cis*-vicinal glycol to produce the 5-membered ring between the axial-equatorial pair, leading to the activation of the 3-OH.[161] This is not observed when it comes to glycosylation reactions, where the 6-OH is the most reactive hydroxyl group. It has also been noticed that the stannylene acetals of lactosides that are typically acylated at the 3'-*O*-position by means of *t*-butyldimethylsilyl chloride afforded only the 6'-*O*-TBDMS ether. The result was explained by a possible equilibrium between the major 3',4'-stannylene and the minor 4',6'-acetal with the latter being displaced by a selective reaction at the most reactive 6'-position, as presented in Scheme 37. TBDMSCl is too bulky to react with the activated 3'-oxygen and reacts with the less sterically hindered 6'- oxygen.[169] Possibly, in the glycosylation reaction a similar behavior could be expected.

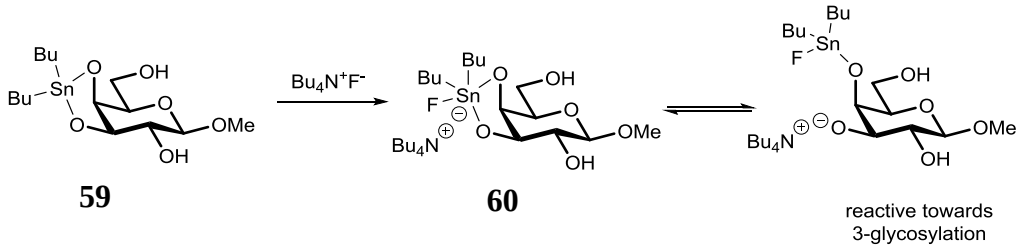
In 2003 another study made by Kaji and co-workers was published.[170] The group demonstrated that the reactivity of different stannylenes can be influenced by

adding a salt, which in this case is tetrabutylammonium fluoride. In Scheme 38 glycosylation of the stannylene derivative of galactopyranoside **52** with per-*O*-pivaloyl-α-D-glucopyranosyl bromide **58** in the presence of $Bu_4N^+F^-$ is shown. The reaction resulted in a 20:1 mixture of the β(1→3)- and β(1→6)-linked disaccharides in a 42% combined yield.



Scheme 38 Regioselectivity shift by means of fluoride ion.[170]

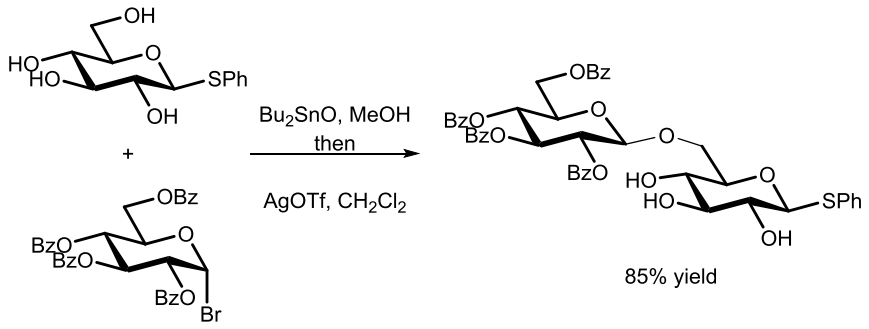
A proposed mechanism for the regioselectivity shift is depicted in Scheme 39.



Scheme 39 Mechanism of Bu_2SnO/F^- ion-mediated glycosylation.[170]

Adding the fluoride ion to the stannylene acetal **59** would generate pentacoordinated complex **60** and then the alkoxide ion at the 3 position reacts with the glycosyl donor to form the β(1→3)-linked disaccharide.[171]

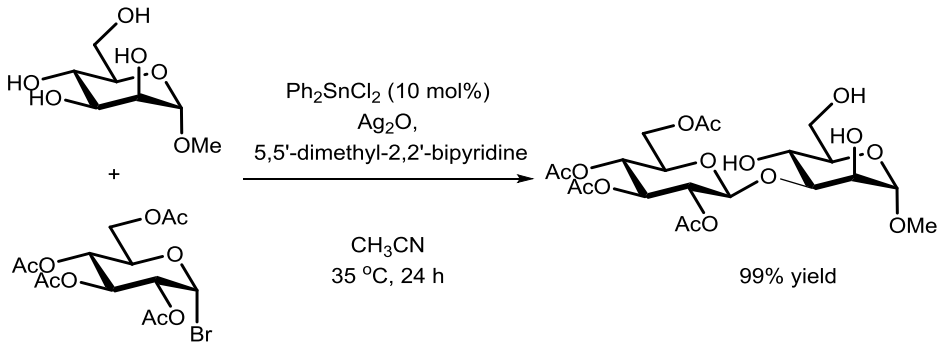
More recently in Robert Madsen's group dibutyltin oxide was used in regioselective glycosylations to form (1→6)-linked glycosides.[172] The model reaction is shown in Scheme 40.



Scheme 40 Example of tin –mediated glycosylation.[172]

Different unprotected phenyl thioglycoside acceptors were glycosylated with glycosyl bromides of glucose, galactose, mannose and glucosamine to give the corresponding (1→6)-linked disaccharides in yields up to 85%. Silver triflate (AgOTf) was used as a promoter in the glycosylation. Initial optimization of the reaction showed formation of the orthoester, when collidine was used as an additive. Use of the weaker base 1,1,3,3-tetramethylurea gave a mixture of several products. Finally, the best yields were obtained with 4Å MS as a desiccant and a very weak acid scavenger.[172]

Another tin species, namely Ph_2SnCl_2 was successfully used in catalytic amounts in the study made by Muramatsu and Yoshimatsu and the model reaction is shown in Scheme 41.[173]



Scheme 41 Regio- and stereoselective glycosylation of methyl α-D-mannopranoside catalyzed by Ph_2SnCl_2.[173]

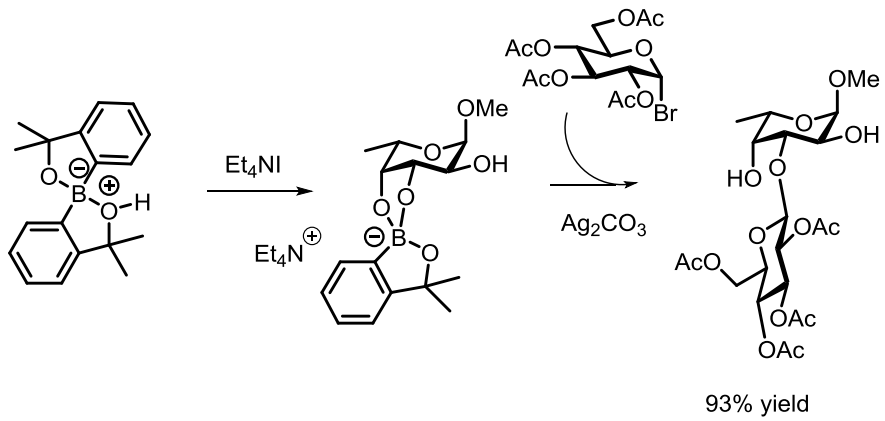
During the further investigation, excellent regioselectivity for the 3-positin and a high yield was observed when derivatives of galacto-, manno-, fuco- and glucopyranosides were used as acceptors. A control experiment in the absence of the

tin catalyst was also carried out, but the reaction did not afford any product, including a disaccharide.[173]

2.5.2 Boron-mediated glycosylations

Selective functionalization of sugars is based on tedious protection/deprotection procedures, which rely mostly on deactivation of hydroxyl groups that are not supposed to undergo glycosylation and leaving one hydroxyl group unprotected, where the glycosylation should occur.
An alternative approach would involve complexation-induced activation of a particular hydroxyl group. This method was successfully applied by the use of tin reagents in the selective glycosylation of unprotected carbohydrates.

The first synthetic application of boronic acid was reported by Oshima *et al.*[174] in 1999. Cyclized 2-(2-hydroxy-2-propyl) phenylboronic acid was used as a promoter for regioselective glycosylation of unprotected methyl fucoside with acetobromoglucose in the presence of tetraethylammonium iodide, silver carbonate and 4 Å MS as shown in Scheme 42.

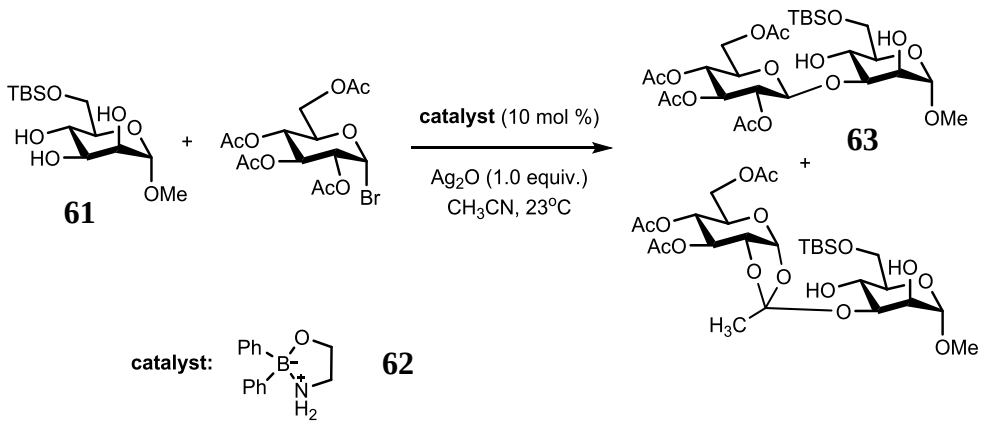


Scheme 42 Regioselective glycosylation with cyclized phenylboronic acid.[174]

The yield of the reaction reached 93% of the corresponding β(1→3)-linked product when the donor to acceptor ratio was 3.5. The presence of the quaternary ammonium salt was found to be essential. Without the salt, formation of the orthoester was observed. In the example shown in Scheme 42, the 3,4-boronate complex is formed and the glycosylation takes place at the 3-position, which has a less hindered equatorial oxygen. Oshima *et al.*[174] used also an octyl glucoside in the reaction and

in this case, a 4,6-boronate was formed, leading to glycosylation at the 6–position. Both mannoside and galactoside gave low selectivity, because of the presence of two diol systems able to form a boronate complex.

In 2011 Taylor *et al*.[175] published another boron compound useful in the regioselective glycosylation. The reaction is shown in Scheme 43.



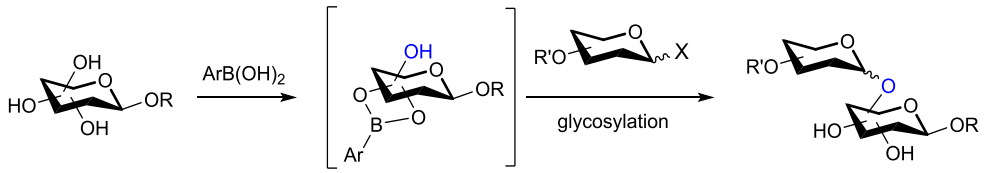
Scheme 43 Example of glycosylation with borinic ester as a catalyst.[175]

The organoboron catalyst was used to promote a regioselective Koenigs-Knorr glycosylation of the mannose acceptor **61**. The primary position in the mannose derivative was protected to avoid difficulties rising from the possible binding of the organoboron catalyst to O4 and O6.[176] When diphenylborinic acid 2-aminoethyl ester **62** was used, the only observed product was the β(1→3)-linked disaccharide **63**, which was isolated in 99% yield. In the same way, 6-*O*-TBS protected methyl α- and β-D-galactopyranoside as well as methyl α-L-fucopyranoside and β-D-arabinopyranoside were glycosylated at the 3-position in high yield.[175] Mechanistic studies proposed that the borinate works as a precatalyst, from which the ethanolamine ligand is displaced under the reaction conditions. The borinic acid catalyst then activates *cis*-diol groups towards electrophilic attack.

Other boron catalysts including phenylboronic acid resulted in the formation of different byproducts, such as the orthoester. Insoluble silver (I) oxide was found to be the best promoter for the glycosylation and gave higher yields then e.g. silver (I) carbonate and silver (I) triflate.

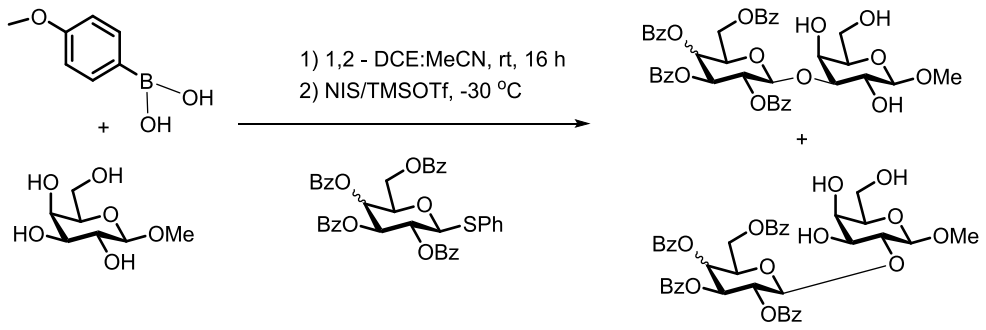
The examples mentioned above show the activating ability of boron reagents. On the contrary, the use of arylboronic acids is an alternative procedure that works by masking the corresponding hydroxyl groups.[177] Derivatives of boronic acids can

form cyclic boronates from *cis*-1,2-diols, including the 4,6-position in carbohydrates. Hence, they can act as a momentary protecting group and the donor can attack the most reactive free hydroxyl group leading to a regioselective glycosylation. The method is shown in Scheme 44.[178]



Scheme 44 Regioselective glycosylation with boronate masking method.[178]

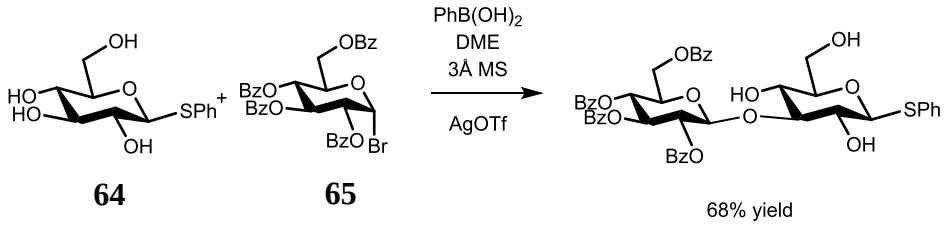
One of the first who focused on the deactivation of certain groups in unprotected carbohydrates was Kaji and co-workers.[178, 179] They showed easy access to (1→3)-linked disaccharides starting from unprotected methyl β-D-galactopyranoside, as shown in Scheme 45.



Scheme 45 Example of glycosylation performed by Kaji *et al.*[178]

The 4,6–diol moiety was masked and therefore deactivated transiently by employing an arylboronic acid. Glycosylation of the 2,3–diol structure favored the β(1→3)-linkage for glucose and galactose and the α(1→3)-linkage for mannose donors. For the galactose acceptor, the β(1→3)-linked product was obtained predominantly due to steric effects, where the electrophiles seem to attack the 3-hydroxyl group in preference to the 2-hydroxyl group. In the β-galactoside there would be more space around the 3-OH position because of the neighbouring axial hydroxyl group at 4 position.

Recently in Madsen's group, regioselective glycosylation of unprotected carbohydrates with phenylboronic acid was also studied.[65] The model reaction is shown in Scheme 46.



64 **65**

Scheme 46 Example of glycosylation with phenylboronic acid.[65]

Thioglycoside acceptor **64** was mixed with phenylboronic acid in 1,2-dimethoxyethane (DME) in the presence of 3 Å MS to give the corresponding 4,6-phenylboronate. The boronate complex was then subjected to a Koenigs-Knorr glycosylation with 2,3,4,6–tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**65**) and with AgOTf as the promoter to give the β(1→3)-linked disaccharide as the only product. Different thioglycoside acceptors were prepared and the boronates were formed in the same way. The boronate structures were characterized by NMR spectroscopy and it was found out that galactoside and 2-aminoglucoside both gave 4,6-boronates. Rhamnoside and fucoside gave 2,3- and 3,4-esters, respectively. On the other hand, mannopyranoside could also form the boronic ester but the ester was not soluble in DME and further studies were not performed.

In summary, the literature background shows that an extensive work has been done in the oligosaccharide synthesis with partially protected and unprotected carbohydrates. Only few cases demonstrate that completely unprotected carbohydrates can be used in the glycosylation. Otherwise, partial protection and metal chelation have to be employed to obtain regioselective products in the glycosylation.

Despite many years of investigation for a universal method to glycosylate unprotected carbohydrates, there is still room for improvement and the development of novel procedures is highly desirable.

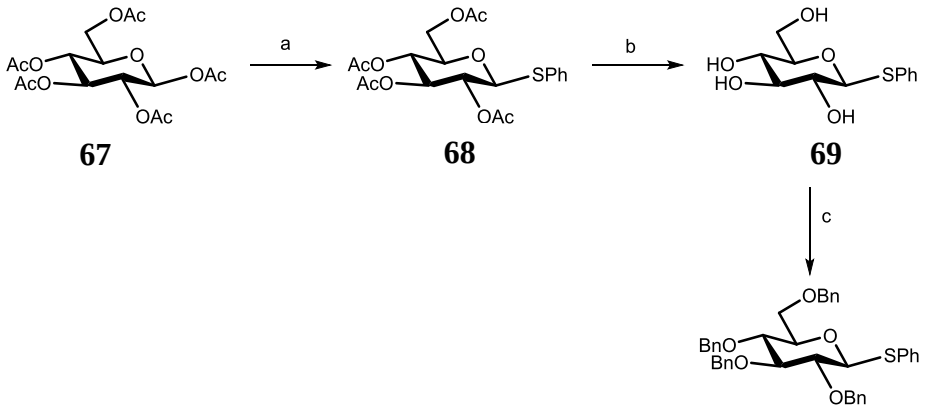
3 Results and discussion

3.1 Halide-mediated glycosylation

3.1.1 Synthesis of glycosyl donors

The aim of the project was to develop a method for regioselective glycosylation with the use of unprotected carbohydrates. Recently, in Robert Madsen's group the emphasis was placed on glycosylations with unprotected carbohydrates via the Koenigs-Knorr protocol. Tin- and boron-mediated glycosylations that led to 1,2-*trans* glycosides were successfully developed.[65,172] The goal of this project was to look closer into 1,2-*cis* glycosylations, also with the use of unprotected carbohydrates. For this purpose, the Lemieux *in situ* anomerization protocol[6] will be employed for the glycosylation reaction.

Perbenzylated glucopyranosyl bromide was chosen as a donor for the research. This donor does not have a participating group at C-2, and therefore the glycosylation should lead to the 1,2-*cis* product. The bromide donor could be prepared from phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**66**). Synthesis of the latter is shown in Scheme 47, according to the procedure found in the literature and with the yields obtained in the present work.[180, 181, 182]



67 **68** **69** **66**

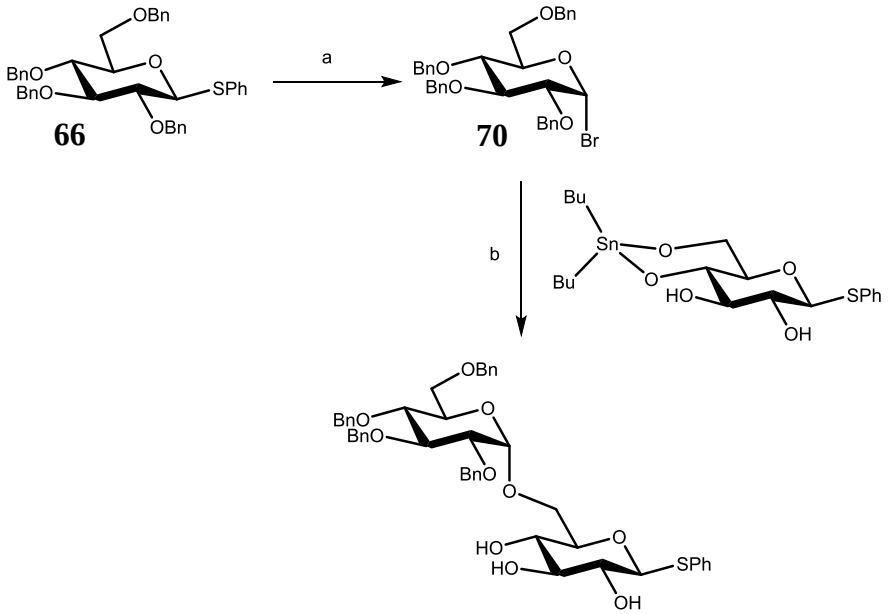
a: *thiophenol, $BF_3 \cdot Et_2O$ (82%);* **b:** *Na in MeOH (quantitative);* **c:** *BnBr, NaH, TBAI, DMF (76%)*

Scheme 47 Synthesis of phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside.[180, 181, 182]

Commercially available 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**67**) was converted to the thioglycoside by using thiophenol in the presence of boron trifluoride etherate as a Lewis acid and the newly formed phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**68**) was isolated in a 82% yield. Next, the acetyl groups were removed in the Zemplén reaction by freshly prepared sodium methoxide and the compound **69** was reacted with benzyl bromide in dimethylformamide in the presence of sodium hydride and tetrabutylammonium iodide to afford the corresponding per-*O*-benzylated thioglycoside **66**. The addition of TBAI ensures a Finkelstein reaction to afford benzyl iodide *in situ*, which reacts in a S_N2 reaction with the alkoxide from the corresponding alcohol.

The reaction was typically performed in dimethylformamide, which is a polar aprotic solvent that favors S_N2 reactions. The disadvantage of the solvent is its boiling point and therefore the complete removal of the solvent on the usual rotary evaporator is challenging. According to the procedure used in this work, the benzylated species is crystallized after adding acetic acid and water to the mixture. The thioglycosides **68** and **69** are also isolated by crystallization, which makes the synthesis easier and faster.

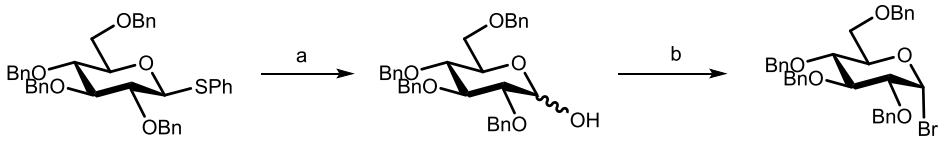
In the literature, benzylated halide donors are usually described as unstable compounds, which are difficult to characterize.[93,183] For that reason, the first attempt for their preparation assumed an *in situ* approach and is shown in Scheme 48.



a: *Br_2, CH_2Cl_2*; **b:** *Bu_4NBr, DMF, CH_2Cl_2 (8%)*

Scheme 48 Formation of the donor in situ and glycosylation.

The benzylated thioglycoside **66** was dissolved in dichloromethane, cooled to 0 °C and titrated with bromine. The reaction was monitored by thin layer chromatography (TLC). After a couple of hours, TLC was showing the presence of the thioglucoside, the bromide donor and small amounts of hydrolyzed donor. At that point, the preformed stannylene acceptor was added to the reaction, followed by tetrabutylammonium bromide. The acceptor was prepared according to the procedure used earlier in the group, by refluxing the unprotected phenylthioglycoside with dibutyltin oxide in methanol.[172] After 24 hours, the reaction was subjected to column chromatography and the α(1→6)-linked disaccharide was isolated in a 8% yield. The majority of the isolated material was phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**66**) but some 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**70**) was also obtained. This experiment showed that the bromide donor is in fact stable enough to survive the column chromatography. The starting material **66** was then converted into the bromide in a two-step procedure, as shown in Scheme 49.



66 **71** **70**

a: *NBS, acetone/water (88%);* **b:** *oxalyl bromide, CH_2Cl_2 (85%)*

Scheme 49 Synthesis of the glucosyl bromide.

The first reaction was the removal of the thiophenol from the anomeric position. This was easily done by using NBS in acetone/water and monitoring the color of the reaction as described by a group at University of Copenhagen.[184] After NBS addition, the reaction mixture becomes yellow and the color disappears after 10-15 minutes. Compound **71** was purified by column chromatography and carefully dried before the next step. After thorough co-evaporation with toluene, compound **71** was dissolved in dry dichloromethane and oxalyl bromide was added carefully to afford the bromide.

Previous syntheses of **70** have included dimethylformamide in the reaction to form a Vilsmeier-type salt,[185,186] but in our hands the bromination worked equally well in the absence of the amide, as in the procedure used by Thiem and Matwiejuk.[146] As mentioned above, removing even small amounts of dimethylformamide in our conditions would lead to extended evaporation and possible hydrolysis of the bromide. The donor was stored in the freezer at -15 °C and under these conditions it was stable for at least two months.

Several groups[185, 146, 186] reported preparation of the halide donor from the hemiacetals, but none of them decided to purify the donor by column chromatography. The reaction was worked-up, the solvent removed by evaporation and the product was directly subjected to the glycosylation.

The quality of oxalyl bromide turned out to be important for fast and clean formation of **70**. The reagent has been stored in a cool, dry place and kept tightly sealed to preclude contact with moisture in order to avoid decomposition to CO, CO_2 and HBr. With a fresh sample, the reaction could take 20 minutes, while a more decomposed oxalyl bromide prolonged the time of the reaction to even 4 hours. Unfortunately, in both cases some amounts of the starting material have been observed. Therefore, the reaction was purified by silica gel flash column chromatography with ethyl

acetate/heptane in order to give the bromide donor in around 85% yield as a slightly yellowish oil.

The same synthetic pathway as described in Scheme 47 and Scheme 49 was applied to the synthesis of the next donors. The corresponding mannosyl and galactosyl bromide, as well as glucosyl chloride, were synthesized and are shown in Figure 10.

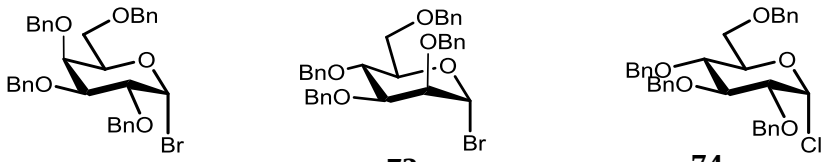
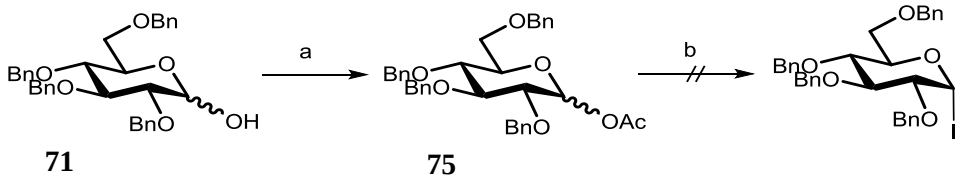


Figure 10 Galactosyl and mannosyl bromide and glucosyl chloride.

Synthesis of the galactosyl bromide **72** gave the product in a high 87% yield but mannosyl bromide **73** was isolated in only a 46% yield. For the synthesis of the chloride, oxalyl chloride was used and the halide donor **74** was formed in a 75% yield.

Next in the line was the synthesis of the iodide donor. As mentioned before, Thiem and Meyer[78] reported that glycosyl acetates, methyl glycosides and 1,6–anhydrosugars are undergoing a reaction with trimethylsilyl iodide (TMSI) to form α-glucosyl iodides. This protocol was also used by Gervay-Hague *et al.*[80] and so far it is the most commonly found method of glycosyl iodide formation in the literature, probably due to the fact that the only by-product is the volatile trimethylsilyl acetate. The synthesis started from **71** by acetylation of the anomeric hydroxyl group. The dry product was then dissolved in anhydrous dichloromethane under nitrogen and the mixture was cooled to 0 °C. Afterwards, TMSI was carefully syringed into the reaction mixture. The synthetic steps are shown in Scheme 50. Handling of TMSI required significant caution because the reagent is very sensitive to light, air and moisture and it fumes hydrogen iodide in air due to the hydrolysis. Therefore, the reagent was stored and added in the darkness.



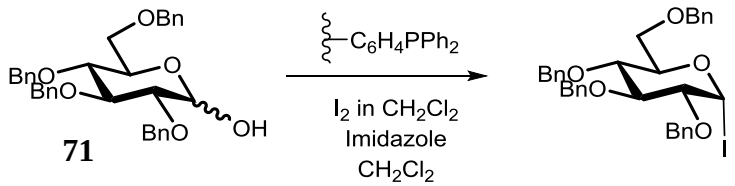
71 **75**

a: *Ac_2O, pyridine (55%);* **b:** *TMSI, CH_2Cl_2*

Scheme 50 Synthesis of iodide donor.

However, the synthesis of the iodide was not successful. It was possible to observe the formation of a new spot on the TLC, which presumably could be the glycosyl iodide. The reaction was followed by azeotropic evaporation with anhydrous toluene, until a colorless distillate persisted. At that point, a sample for NMR analysis was taken out but the iodide donor was not observed. The main product observed was 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**75**) and hydrolyzed donor, i.e. **71**.

Having isolated the starting material **75** as a major product of the reaction, another method that is not employing TMSI was chosen in an attempt to form the iodide. In 1999, Caputo *et al.*[73] described a mild synthesis of glycosyl iodides, where time-consuming work-up and purification is avoided, as shown in Scheme 51.



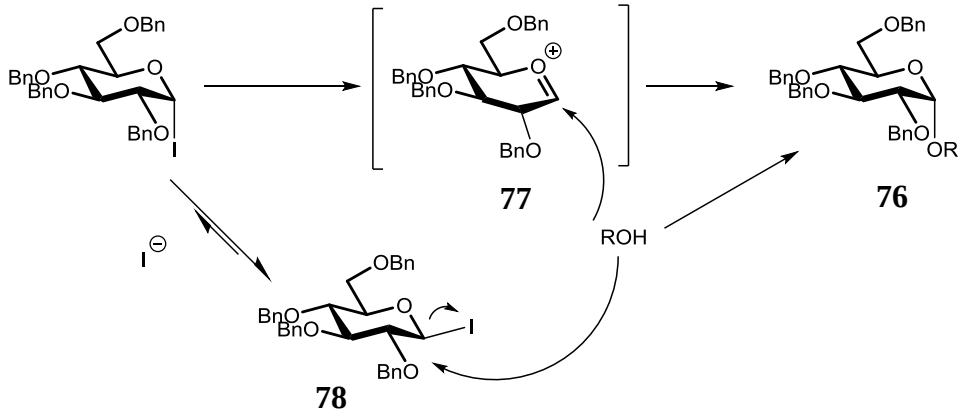
Scheme 51 Formation of α-D-glycosyl iodide according to Kunz and Caputo.[73]

The reagent used in the synthesis is a complex of polystyryl diphenylphosphine and iodine prepared *in situ* in dry CH_2Cl_2 at room temperature. The formed complex is a good electrophile toward oxygen nucleophiles and its effectiveness is enhanced by the presence of imidazole, which role is to trap protons released during the reaction. Two equivalents of imidazole per phosphine were used, because in the aprotic CH_2Cl_2, protonated imidazole is a relatively strong acid and a hydrogen-bonded dimer of imidazole could be an actual neutralizing species.[73]

2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**71**) was added as the last compound to the reaction mixture and the reaction was monitored by TLC. The formation of a new spot was observed again, but when the TLC was repeated, the new spot had

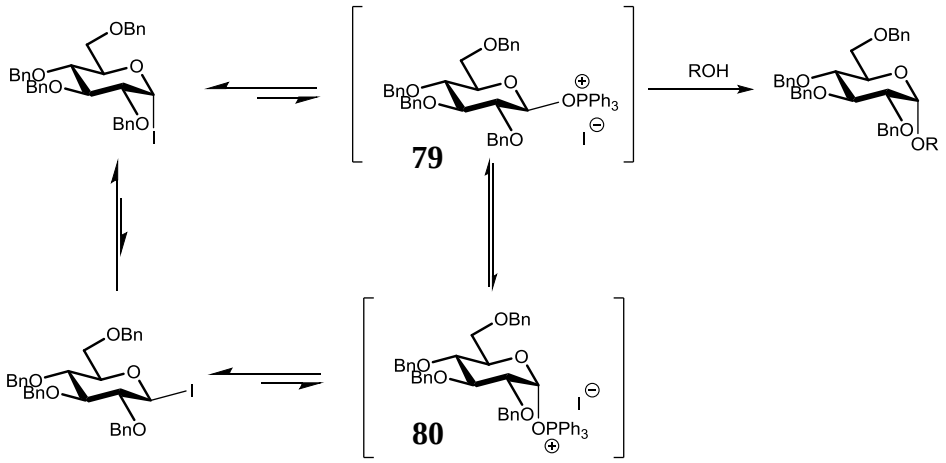
disappeared and only the starting material was present. The reaction mixture was filtered and an NMR experiment showed presence of the starting material. However, there was a possibility that the preparation of the sample and conducting the NMR experiment were taking too long and the iodide donor therefore was not observed. Thus, the subsequent glycosylation was performed with the possible iodides, prepared in the way described in Scheme 50 and Scheme 51. To the donors, anhydrous dichloromethane and phenyl 4,6-*O*-(dibutylstannylene)-1-thio-β-D-glucopyranoside were added and the glycosylation with two different promoters was conducted.

First, tetrabutylammonium iodide was tried as a promoter and the mechanism of this reaction is shown in Scheme 52. The mechanism of the reaction is based on the earlier work of Lemieux and it is assumed that tetrabutylammonium iodide catalyzes the rapid interconversion of the α- and β-iodides. The α-glycoside **76** is then formed by preferential attack on the oxocarbenium ion **77** from the bottom face of the ring. Another possibility is the attack of the neutral alcohol on the more reactive β-iodide **78**, via an S_N2-like displacement.[6]



Scheme 52 Mechanism of glycoside formation by means of TBAI. [71]

In the second reaction, triphenylphosphine oxide[187,188] was used as a promoter and the mechanism of the reaction is shown in Scheme 53.



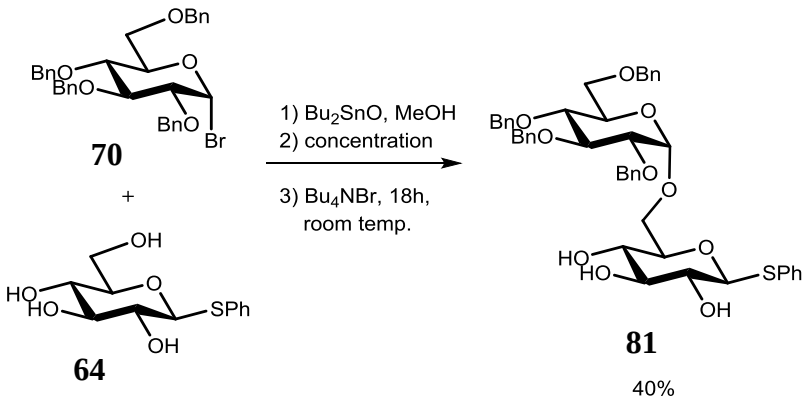
Scheme 53 Mechanism of glycoside formation by means of triphenylphosphine oxide.[189, 71]

The promoter activates the iodide donor and neutralizes the hydrogen iodide formed during the course of the reaction. Therefore, adding a base to maintain neutral conditions is redundant. Additionally, the use of the phosphine oxide minimizes elimination from the glycosyl iodide to form a glycal by-product, which could complicate the purification of the product. In the D-glucopyranose series, the α-selectivity probably arises due to S_N2 attack on the more reactive β-D-glucosyl oxyphosphonium iodide **79**. This species has not been observed by NMR experiments which indicates, if present, only very small amounts of this reactive intermediate exist in an equilibrium with α-D-glycosyl iodide **80** and the phosphine oxide.[71]

From both reactions, 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**75**) and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**71**) were isolated, and no trace of a coupling product was observed. Since these results were not promising it was decided not to investigate the iodide donors in further detail.

3.1.2 Optimization of glycosylation

Unprotected phenyl 1–thioglycopyranosides were chosen as acceptors for the optimization studies in line with earlier work in Robert Madsen's group,[65, 172] since the regioselective glycosylation would then provide a straightforward way to a number of thioglycoside building blocks that are useful glycosyl donors. In Scheme 54, a reaction between glucosyl bromide and phenyl 1-thio-β-D-glucopyranoside is shown.



Scheme 54 Glycosylation between glucose donor and glucose acceptor.

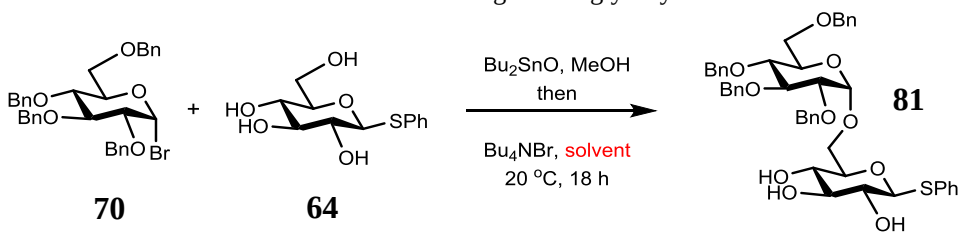
The regioselective coupling of **70** to phenyl thioglucoside **64** was performed by treating the latter with 1 equivalent of dibutyltin oxide in methanol followed by the removal of the solvent and drying under high vacuum.[172] The resulting stannylene acceptor complex was then dissolved in dichloromethane with 1.8 equivalent of donor **70** and 1.8 equivalent of Bu_4NBr. After stirring overnight at room temperature the (1→6)-linked disaccharide **81** was isolated in a 40% yield as the pure α anomer with the unreacted donor, a small amount of hydrolyzed donor and the unreacted acceptor as the only remaining compounds in the mixture. The regioselectivity observed for the glycosylation of phenyl 1-thio-β-D-glucopyranoside (**64**) corresponds to that observed in earlier tin-mediated couplings of β-D-glucopyranosides.[166] In the case of the β-D-glucopyranosides, where the *cis*-vicinal glycol system is not present, only the most reactive primary group is activated[161] and therefore glycosylation led to (1→6)-linked product formation. In fact, other coupling products were not observed and this indicates that the desired reaction is very stereo- and regioselective under these conditions. However, it is also a quite

slow transformation and the coupling was therefore subjected to a further optimization.

3.1.2.1 Solvent studies

The nature of the solvent is known to have an effect on stereoselectivity and yield of the glycosylation reaction. Generally, if the synthesis of α-glycosides is desired, dichloromethane, 1,2-dichloroethane or toluene would be suitable candidates as the reaction solvents. However, as mentioned in **2.3**, solvents can also participate in the glycosylation reaction and alter the stereoselectivity. Ether-type solvents like diethyl ether, dioxane and THF have a tendency to shift stereoselectivities towards *cis*-glycosides.[26, 86] In Lemieux's original study on the halide-ion catalyzed glycosylation, dichloromethane along with benzene were pointed out as the best solvents for the reaction.[6] The investigation was started with a reaction in dichloromethane but during further studies, more solvents were investigated. The results of these studies are shown in Table 1.

Table 1 Solvent screening for the glycosylation.



70 **64**

Entry	Solvent	Temp. (°C)	Time (h)	Yield of disaccharide (%)
1	CH_2Cl_2	20	18	40
2	THF	20	18	35
3	CH_3CN	20	18	30
4	CH_3CCl_3	20	18	25
5	THF	40	18	45[a]
6	CH_3CN	40	18	30[a]
7	CH_3CCl_3	40	18	18
8	Diethyl ether	20	18	10
9	Dioxane	20	18	18
10	Toluene	20	18	12
11	DMF	20	18	-

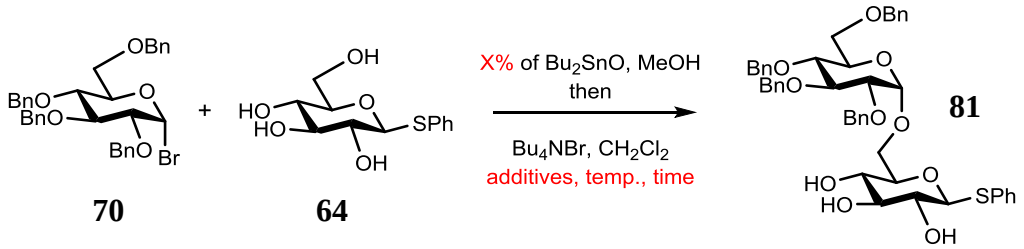
a) α/β mixture of products

Reaction in THF, acetonitrile and trichloroethane produced slightly lower yields than in dichloromethane (Entries 2-4). Increasing the reaction temperature gave better conversion in THF while no improvements were observed in acetonitrile and trichloroethane (Entries 5-7). However, in THF and acetonitrile the product **81** was obtained as a α/β mixture with a ratio of about 10:1 which renders the conditions unattractive. The stannylene acetal complex of the acceptor was not fully soluble in diethyl ether, dioxane and toluene (Entries 8-10) and that possibly led to poor yields

of **81** in these solvents. Lastly, DMF was examined but the use of that solvent led to no conversion at all. The solvent study showed that only THF could be used as an alternative solvent, giving similar results to the reaction that was run in dichloromethane.

Consequently, our attention moved back to dichloromethane and finding optimal conditions for the glycosylation. The optimization conditions are presented in Table 2.

Table 2 Optimization of conditions for the glycosylation in dichloromethane.



70 **64**

Entry	Bu_2SnO (%)	Additives	Temp. (°C)	Time (h)	Yield of disaccharide (%)
1	-	4 Å	20	18	17
2	100	4 Å	20	18	46
3	100	-	20	18	40
4	100	4 Å	reflux	8	10
5	100	4 Å	0	18	8
6	10	4 Å	20	18	35
7	10	-	20	18	30
8	100	Lutidine	20	18	-
9	100	Collidine	20	18	-

In order to determine whether the results obtained are truly due to tin activation, acceptor **64** was directly coupled with donor **70** in the experiment in dichloromethane with molecular sieves (Entry 1). The absence of dibutyltin oxide led to formation of

several by-products and the (1→6)-linked product was isolated in only a 17% yield. This result could originate from the very poor solubility of the acceptor in the reaction solvent. It moreover showed that the stannylene acetal is crucial for the solubility of the acceptor and for the exclusive formation of the (1→6)-linked glycosylation product. The reaction was also repeated in the presence of 4 Å molecular sieves and that increased the yield to 46% (Entry 2). An improvement in the yield of the reaction in the presence of molecular sieves can be explained by considering the removal of traces of water that is released upon tin acetal formation, by the molecular sieves. Furthermore, molecular sieves are slightly basic and may also serve as weak acid scavenger of hydrogen bromide. The reaction was also conducted in the absence of 4 Å MS and that led to formation of the product in 40% yield (Entry 3).

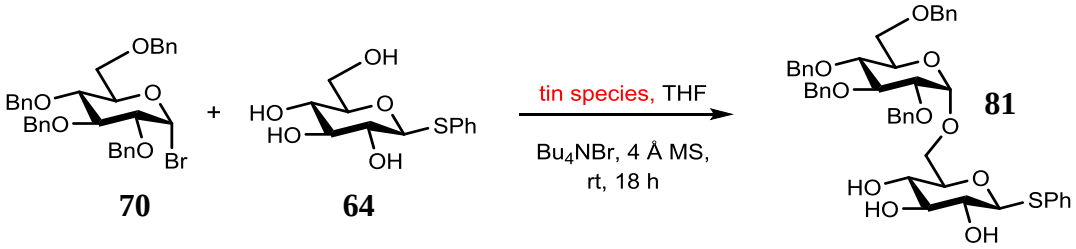
Higher or lower temperature gave a lower yield in the presence of dibutyltin oxide (Entries 4 and 5) and room temperature was therefore selected for general use. Interestingly, the amount of dibutyltin oxide could be lowered to 10% and the disaccharide **81** was still obtained in a poor yield (Entries 6 and 7). However, the acceptor **64** was not fully soluble in dichloromethane upon pretreatment with only a catalytic amount of dibutyltin oxide (Entries 6 and 7) and that probably led to poor yields of the desired product. Molecular sieves were replaced with bases collidine and lutidine but this led to the decomposition of the donor and no product **81** was observed (Entries 8 and 9).

Typically, bases serve as acid acceptors and they provide relevant conditions when highly acid sensitive protecting groups are used. In the case of the halide-mediated glycosylations earlier studies showed that base offers no important catalytic effect and it is not involved in the formation of a reactive intermediate.[6] On the other side, the use of appropriate molecular sieves has proved very effective in trapping the acid and removing water from the reaction mixture.[122, 190] The same observation was made in the course of this work.

3.1.2.2 Studies of different tin species

Over recent years, several tin species have been tested in the regioselective glycosylation of unprotected carbohydrates.[173] Our investigation included two tin chloride species with a different length of alkyl chain and one with an aryl group. Dimethyltin oxide was also chosen in order to have a comparison to dibutyltin oxide, which is widely used in the research in Robert Madsen's group. The investigation of the tin species is presented in Table 3.

Table 3 Studies of different tin compounds for glycosylation.



70 **64**

Entry	10% of tin species	Solvent	Time (h)	Yield of disaccharide (%)
1	Bu_2SnCl_2	THF	18	25
2	Ph_2SnCl_2	THF	18	18
3	Me_2SnCl_2	THF	18	8
4	Me_2SnO	THF	18	-

Tin chlorides were tested first in the glycosylation (Entries 1-3). In order to form the stannylene acetal by using a tin chloride, it was only required to stir with the acceptor for a short time. After that, the glycosyl donor and tetrabutylammonium bromide were added to the reaction mixture. Compared to refluxing the acceptor with dibutyltin oxide and then drying the stannylene acetal complex under high vacuum, a significant amount of time could be saved. Moreover, only catalytic amounts of tin chloride were used. Unfortunately, the best yield obtained was 25% (Entry 1) and it was clear that tin chlorides could not replace dibutyltin oxide in the developed method. Again, all organotin compounds led to the formation of one product only, which was the 1,6-linked disaccharide. Earlier studies of Muramatsu and co-workers

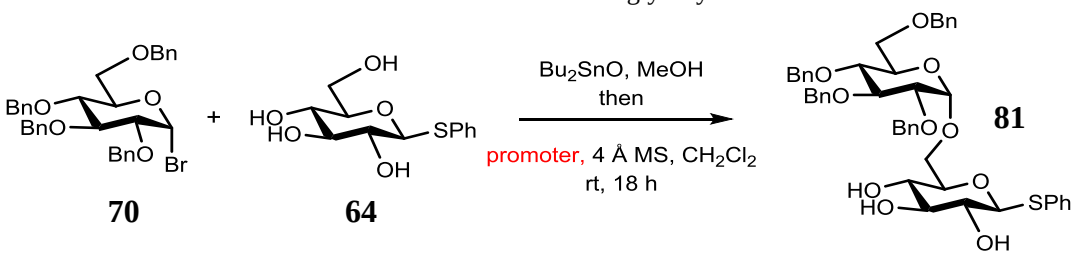
showed that the use of an organotin catalyst with different alkyl chain lengths could influence selective functionalization of unprotected monosaccharides.[191,192] In addition, another report described glycosylation with Ph_2SnCl_2 that leads to the selective formation of 1,3-linked disaccharides under Koenigs-Knorr conditions.[173] That was not the case in our glycosylation, where only one 1,6-linked disaccharide was observed with no traces of other coupling products. Reaction with Me_2SnO was also performed but the stannylene complex with the acceptor formed in that way was not soluble in dichloromethane or THF or other common solvents (Entry 4).

3.1.2.3 Promoter studies

Synthetic methods for the glycosylation require activation of the carbohydrate donor. Because of the broad scope of glycosylation reactions, there is a continuous need for new promoters to adjust the reaction for specific donors and acceptors. A number of promoters are heavy metal based and the disadvantage is the generated waste. To avoid heavy metal waste, $BF_3{\cdot}OEt_2$ and TMSOTf are used as common alternatives.

However, in the halide-mediated glycosylation, tetraalkylammonium halides are the standard promoters of choice. Table 4 contains a few other promoters that were investigated in the glycosylation.

Table 4 Promoters used in the glycosylation.



Entry	Promoter	Solvent	Time (h)	Yield of disaccharide (%)
1	Bu_4NI	CH_2Cl_2	18	42
2	I_2	CH_2Cl_2	18	-
3	I_2/DDQ	CH_2Cl_2	18	32[a]
4	$ZnBr_2$	CH_2Cl_2	18	-

a) α/β mixture of products

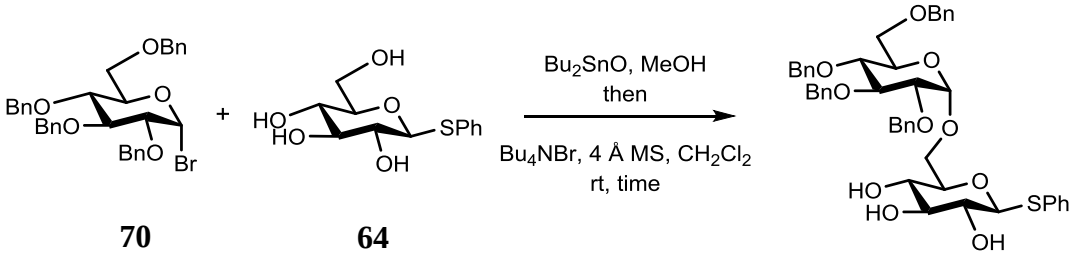
Replacing Bu_4NBr with Bu_4NI (Entry 1) gave no improvement in the reaction yield. This result was disappointing because of the reported superiority of tetrabutylammonium iodide compared to tetrabutylammonium bromide.[74] The stronger activators like I_2[193] and zinc (II) bromide[194] (Entries 2 and 4) gave mixtures of donor and hydrolyzed donor and other products that have not been further investigated. That result was acceptable because it is generally known that halide ion glycosylation gives the best results when milder activating conditions are used.[195] Lastly, the reaction with I_2/DDQ[193] (Entry 3) was performed and it gave similar yields as the reaction with Bu_4NBr, but now as a 2:3 α/β mixture.

3.1.2.4 Further optimization and synthesis of various unprotected acceptors for the glycosylation

In all these experiments with dibutyltin oxide the remaining material in the mixture was an unreacted donor and acceptor. In addition, earlier studies on the halide-mediated glycosylation showed that steric hindrance of the hydroxyl group of the reacting alcohol was found to decrease the rate of the reaction. The reaction with methanol was about two times faster than the reaction with isopropyl alcohol and

about ten times faster than the reaction with *t*-butyl alcohol. Further examination indicated that a reaction time of 2 to 4 days might be needed.[6] For that reason, it was decided to extend the reaction time from 24 h to 72 h and the results are shown in Table 5.

Table 5 Yields of regioselective glycosylation with glucose donors and acceptor.



70 **64** **81**

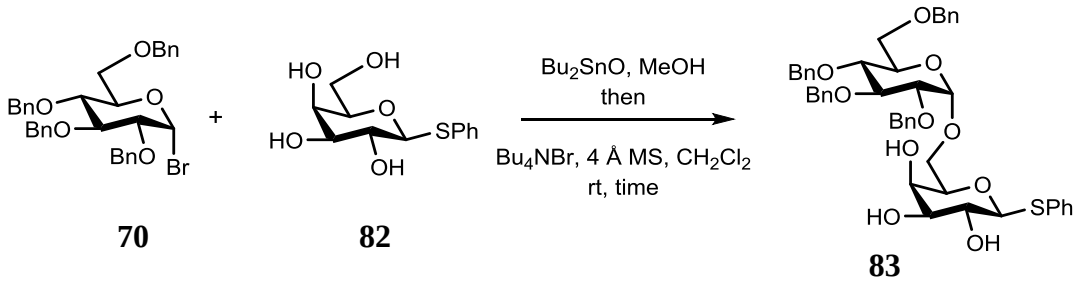
Entry	Donor	Acceptor	Bu_2SnO (%)	Time (h)	Product	Yield of disaccharide (%)
1	**70**	**64**	100	24	**81**	50
2	**70**	**64**	100	72	**81**	56
3	**70**	**64**	10	24	**81**	40
4	**70**	**64**	10	72	**81**	46
5	**74**[a]	**64**	100	72	**81**	45

a) Benzylated chloride donor **74** from **Figure 10** was used in the reaction.

Extending the reaction time produced **81** in a 50% yield after 24 h and a 56% after 72 h (Entries 1 and 2). Both yields were lowered by 10% to give 40% and 46%, respectively, when only a catalytic amount of dibutyltin oxide was used (Entries 3 and 4). Replacing the bromide with the corresponding chloride **74** also gave a lower yield of **81** due to a slower conversion (Entry 5).

In the next reaction a galactose acceptor was employed and the results of the glycosylation are shown in Table 6.

Table 6 Yields of regioselective glycosylation with glucose donor and galactose acceptor.



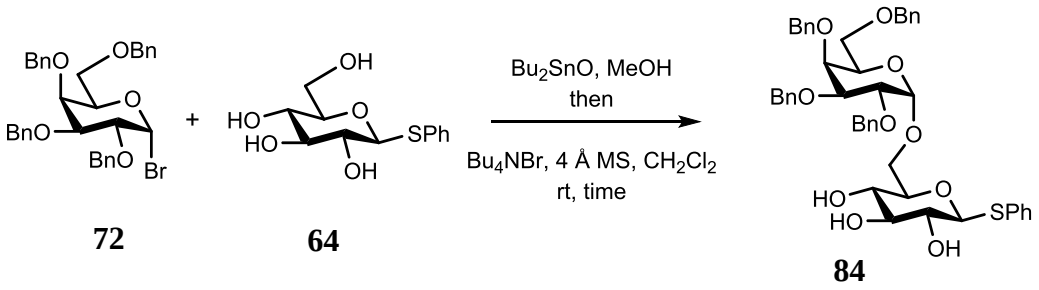
70 **82** **83**

Entry	Donor	Acceptor	Bu_2SnO (%)	Time (h)	Product	Yield of disaccharide (%)
1	**70**	**82**	100	24	**83**	52
2	**70**	**82**	100	72	**83**	58
3	**70**	**82**	10	24	**83**	42
4	**70**	**82**	10	72	**83**	50

When the optimized conditions were applied for coupling between **70** and galactose acceptor **82**, disaccharide **83** was produced in a 52% yield after 24 h and 58% after 72 h (Entries 1 and 2). Again, a decrease in yield was observed when the glycosylation was performed with only a catalytic amount of dibutyltin oxide, where the reaction yielded 42% after 24 h and 50% after 72 h, respectively (Entries 3 and 4). The use of a catalytic amount of the tin species decreased the solubility of the acceptor as compared to the optimized conditions and that possibly led to a lower yield of the product.

In the next glycosylation, a galactose donor has been prepared and the results of the coupling with the glucose acceptor are shown in Table 7.

Table 7 Yields of regioselective glycosylation with galactose donor and glucose acceptor.



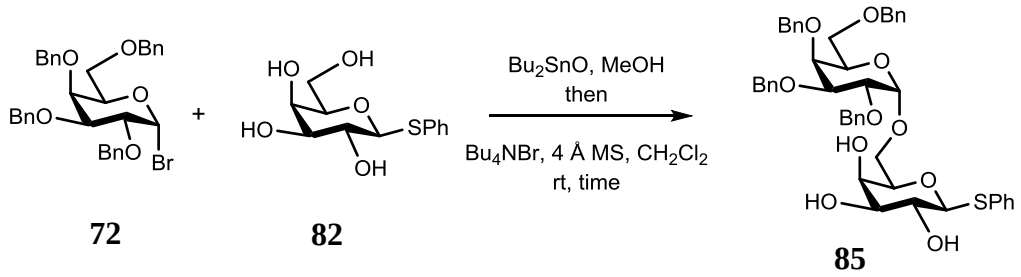
72 **64** **84**

Entry	Donor	Acceptor	Bu_2SnO (%)	Time (h)	Product	Yield of disaccharide (%)
1	**72**	**64**	100	24	**84**	48
2	**72**	**64**	100	72	**84**	57
3	**72**	**64**	10	24	**84**	39
4	**72**	**64**	10	72	**84**	44

The reactions of galactose donor **72** and glucose acceptor **64** were performed with both stoichiometric and catalytic amounts of dibutyltin oxide and the yields were essentially the same as obtained with the glucose donor. After 24 h the glycosylation yielded 48% (Entry 1) and 39% of **84**, when less dibutyltin oxide was used (Entry 3). The disaccharide was obtained in a 57% yield, when the reaction lasted 72 h and stoichiometric amounts of dibutyltin oxide were used (Entry 2). Decreasing the amount of dibutyltin oxide led to the product in a 44% yield (Entry 4). All the glycosylations under the optimized conditions gave exclusively the α-linked disaccharide and none of the β-isomer were detected.

Finally, a galactose donor and acceptor have been investigated in the glycosylation and the results are shown in Table 8.

Table 8 Yields of regioselective glycosylation with galactose donor and glucose acceptor.



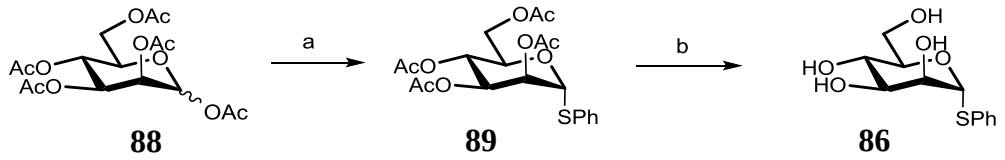
72 **82** **85**

Entry	Donor	Acceptor	Bu_2SnO (%)	Time (h)	Product	Yield of disaccharide (%)
1	**72**	**82**	100	24	**85**	44
2	**72**	**82**	100	72	**85**	52
3	**72**	**82**	10	24	**85**	38
4	**72**	**82**	10	72	**85**	47

The coupling between **72** and **82** produced disaccharide **85** in a 44% yield after 24 h (Entry 1) and 52% after 72 h (Entry 2), when stoichiometric amounts of dibutyltin oxide were used. Disaccharide was obtained in a 38% yield after 24 h (Entry 3) and in a 47% yield after 72 h (Entry 4), when using catalytic amounts of the tin species.

The structures of the disaccharides were interpreted based on ^{1}H and ^{13}C and high resolution mass spectrometry. The preliminary analysis of the interglycosidic linkage was defined by considering the deshielding effect of the ^{13}C chemical shift. For all disaccharides the C-6 carbon atoms resonate at the considerably lower magnetic field, around 68.4 to 69.3 ppm. Compared to the acceptors before the glycosylation, where the C-6 carbon atoms can be found around 61.2 to 62.2 ppm, there is a difference of about 7 ppm.[170] Additional confirmation was obtained by HMBC analysis. For all disaccharides a correlation between the H-6 in the acceptor and the C-1' at the donor anomeric carbon was detected. Furthermore, the anomeric configurations of the disaccharides were determined from the size of $^{3}J_{H}$ coupling constants between H-1' and H-2' that for α-anomers have values between 2.5 to 4.1 Hz.

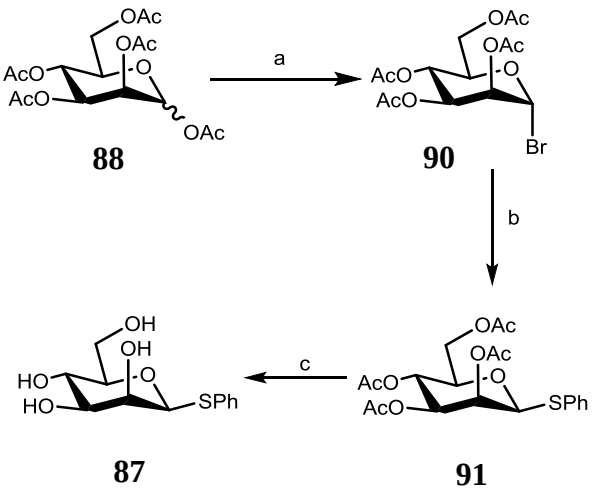
With the mannose donor **73** no reaction occurred under optimized conditions with glucose acceptor **70** and galactose acceptor **72**. This is due to the low reactivity of this donor compared to glucosyl and galactosyl bromide in the halide-mediated glycosylation. Earlier studies on the mannose donor demonstrated very low conversion rate and low yields, unless a large excess of donor was used.[196]
Subsequently, phenyl 1-thio-α-D-mannopyranoside (**86**) and phenyl 1-thio-β-D-mannopyranoside (**87**) were synthesized. The synthesis of phenyl 1-thio-α-D-mannopyranoside (**86**) is shown in Scheme 55.



a: *thiophenol, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (60%);* **b:** *Na in MeOH (quantitative)*

Scheme 55 Synthesis of the phenyl 1-thio-α-D-mannopyranoside.

Thioglycoside **86** was synthesized according to the literature procedure from **88** and **89** in around 80% yield over two steps.[197] The more difficult β-mannopyranoside **87** was synthesized in the way shown in Scheme 56 by slight modification of a literature protocol.[198]



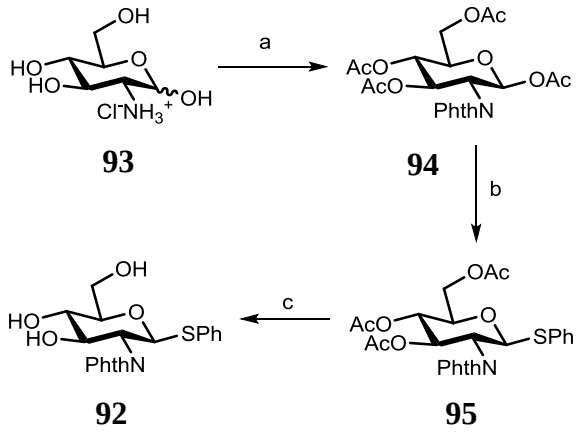
a: *HBr, CH_2Cl_2 (90%);* **b:** *thiophenol, NaH, DMF (85%);* **c:** *Na in MeOH (quantitative)*

Scheme 56 Synthesis of phenyl 1-thio-β-D-mannopyranoside.

For the preparation of **87** the starting material was 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose (**88**), which was prepared from D-mannose. Conditions and problems concerning this synthesis are described later in the thesis. Treatment with HBr gave acetobromomannose **90** in a 90% yield, which was then converted to phenyl β-thioglycoside **91** by using thiophenol in presence of sodium hydride in DMF. The resulting compound was isolated in a 85% yield. In the next reaction, the acetyl groups were removed to form an unprotected mannosyl acceptor **87** in quantitative yield.[198]

Stannylene acetals of α and β thiomannosides were formed in methanol. However, the reactions between them and donors **70** and **83** in dichloromethane only led to decomposed donor and unreacted acceptor after 72 h. The stannylene complexes of **86** and **87** were completely soluble in dichloromethane. Previous studies in the Madsen's group demonstrated that mannose gives a lower yield than glucose and galactose in the regioselective Koenigs-Knorr glycosylation of the corresponding phenyl 1-thioglycosides.[172] A similar difference between the three monosaccharides was observed in the stannylene-mediated *tert*-butyldimethylsilylation of the methyl glycosides at position 6.[199] These results may indicate that mannosides are less inclined to form a 4,6-stannylene acetal than glucosides and galactosides, but instead prefer a 2,3-acetal.[157] Moreover, these acetals can exist as dimers and oligomers in a solution that will probably make the stannylene complexes of **86** and **87** unreactive in the halide-mediated glycosylation.

More acceptors were prepared with the expectation that the solubility of the stannylene complexes of these acceptors in the solvents selected for the glycosylation will be optimal. At first, a glucosamine acceptor was synthesized as shown in Scheme 57, following a literature procedure.[200]

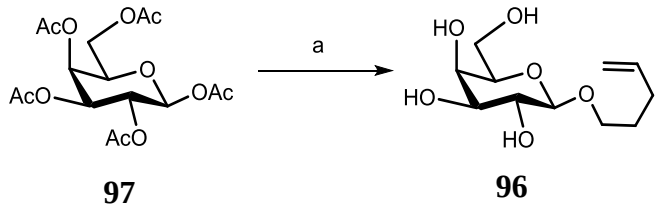


a: *i) NaOMe, MeOH; ii) PhthO, Et_3N; iii) Ac_2O, pyridine (72%);* **b:** *thiophenol, TMSOTf (75%);* **c:** *Na in MeOH (quantitative)*

Scheme 57 Synthesis of glucosamine acceptor.

For the preparation of **92** the starting material was commercially available glucosamine hydrochloride **93**. Glucosamine hydrochloride was converted to acetylated species **94** in a sequence of reactions. First, the hydrochloride was neutralized with freshly prepared sodium methoxide. Finely powdered phthalic anhydride was then added, followed by the addition of triethylamine and methanol to reduce viscosity. The reaction mixture was stirred vigorously to speed up the exchange rate of the reactants between the solid and solution states. Efficient stirring was crucial for the complete conversion of the starting material and obtaining the crude product that was later suspended in pyridine and treated with acetic anhydride. After completing the reaction, work-up and crystallization let to isolation of the product **94** in a 72% yield. The phthalimido protection of glucosamine has been a non-trivial reaction in the field for many years and a 72% yield is therefore a satisfying result. For comparison, the group of Macmillan *et al.*[201] obtained **94** in a 40% yield. 1,3,4,6-Tetra-*O*-acetyl-2-phthalimido-2-deoxy-β-D-glucopyranose (**94**) was converted to the β-thioglycoside **95** in a 75% yield by using trimethylsilyl triflate as a Lewis acid. Next, the acetyl groups were removed by the Zemplén reaction to form the final acceptor **92**.[200]

Then 4-pentenyl galactoside **96** was prepared to be used as an acceptor, as shown in Scheme 58 according to a previous protocol in the group.[202]



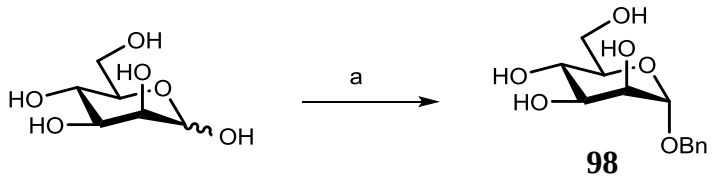
97 **96**

a: *i) pent-4-en-1-ol, $BF_3{\cdot}Et_2O$, CH_2Cl_2; ii) Na in MeOH (60%)*

Scheme 58 Synthesis of 4-pentenyl galactoside.

For the preparation of **96**, galactose pentaacetate **97** was used as the starting material. Treatment with pent-4-enyl alcohol and $BF_3{\cdot}OEt_2$ followed by Zemplén deacetylation gave crystalline pent-4-enyl β-galactoside.

The last acceptor possessed a benzyl group in the anomeric position as presented in Scheme 59 and was prepared by a literature procedure, although in a significantly lower yield.[203]



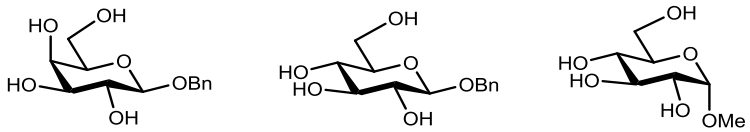
98

a: *BnOH, CH_3COCl (45%)*

Scheme 59 Synthesis of benzyl mannoside.

D-mannose as the starting material was subjected to a Fischer glycosylation at the anomeric carbon with benzyl alcohol and acetyl chloride to give benzyl α-D-mannopyranoside (**98**) in 45% yield.[203] Unfortunately, stannylenes of the acceptors **96** and **98** were not soluble in dichloromethane or THF.

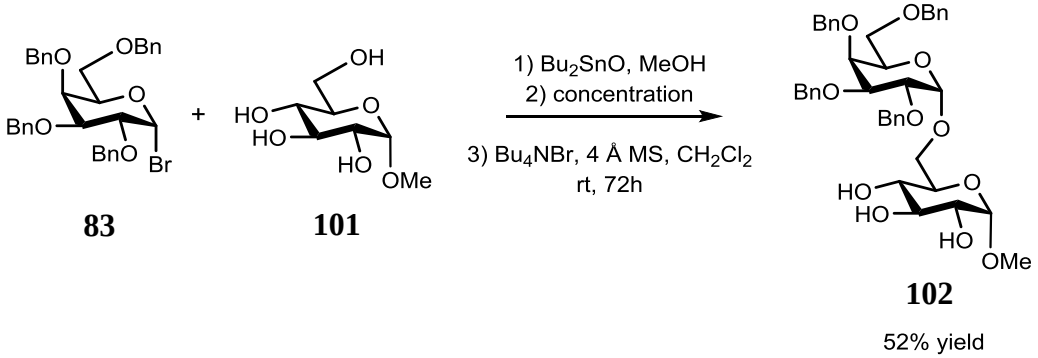
Benzyl β-D-galactopyranoside **99** and benzyl β-D-glucopyranoside **100** were also synthesized according to a literature procedure[204] in a 72% and 67% yield, respectively. Benzyl glycosides **99** and **100** and commercially available methyl α-D-glucopyranoside **101** are shown in Figure 11.



99 **100** **101**

Figure 11 Other unprotected acceptors.

Stannylene complexes of **99** and **100** were formed but unfortunately, they were not soluble in dichloromethane or THF. This was not the case when using methyl α-D-glucopyranoside (**101**), which was fully dissolved after the formation of the tin complex. As a result, glycosylation with donor **83** could be performed and disaccharide **102** was isolated in a 52% yield after 72 h. The reaction is shown in Scheme 60.

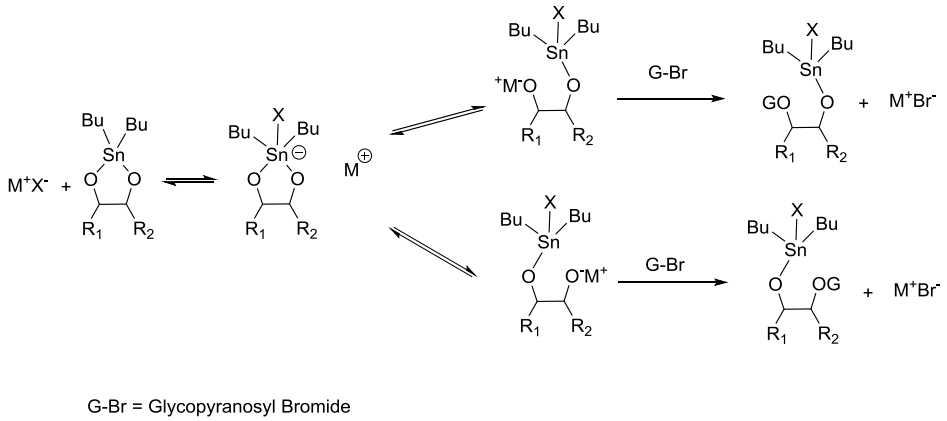


83 **101** **102**

52% yield

Scheme 60 Regioselective glycosylation of **101**.

Exclusive formation of (1→6)-linked products leads to the conclusion that the stannylene acetal formation on the galactosyl and glucosyl acceptors takes place at the 4 and 6 hydroxyl group. The proposed mechanism for the activation of the tin acetal and glycosylation with tetrabutylammonium bromide[205] is presented in Scheme 61.



Scheme 61 A proposed mechanism for the activation of tin intermediates by halides.[205]

The regioselectivity for the stannylene-mediated acetal formation could orginate from a selective Sn-O bond cleavage in the stannylene acetal ring, promoted by a pentacoordinated tin atom.[206, 205] The coordination of the halide anion to the tetracoordinated tin atom enhances the selective Sn-O bond cleavage to give a reactive oxygen anion coordinated to Bu_4N^+, followed by a nucleophilic attack of the oxygen species at an electrophile, in this case the glycosyl bromide. Preferential cleavage of the Sn-O bond as well as the nucleophilicity of the oxygen moiety takes part in the control of regioselectivity of the reaction.

In Figure 12 a possible intermediate with the coordinated tetrabutylammonium cation at the C-6 oxygen is presented.

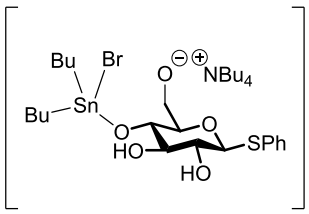


Figure 12 Proposed intermediate with the tetrabutylammonium cation attached to the oxygen at C-6 of the acceptor.

From steric reason, it is more favorable that the bulky tetrabutylammonium cation will surround the oxygen atom at the primary position and then give place for the attachment of the monosaccharide. Moreover, the primary position is also the most reactive one, as compared to the 4-position which on the contrary is often the least reactive.

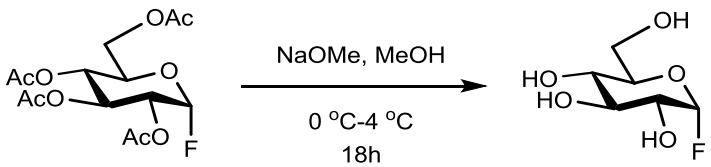
3.1.2.5 Synthesis of unprotected bromide donor

The usual chemical synthesis of oligosaccharides has been relying on the use of *O*-protected glycosyl donors in a block or a stepwise fashion. The possibility of employing unprotected donors in the glycosylation could even further develop the glycosylation protocol for the following reasons:

- Reducing the number of steps in the glycosylation
- Possibility of higher reactivity of unprotected donors compared to the *O*-acyl protected ones because of the absence of the electronic effects caused by the ester groups
- Achieve different stereochemistry at the glyosidic bond due to the absence of protecting groups
- Potential for iterative assembly of saccharide moieties

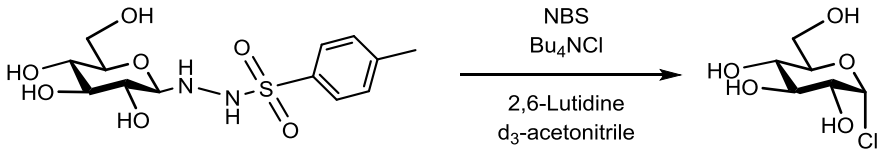
In the literature, there are examples of employing unprotected donors in the glycosylation *e.g.* unprotected 3-methoxy-2-pyridyl (MOP) donors to efficiently afford 1,2-*cis* glycosides[207], an unprotected 4-bromobutyl mannoside donor able to generate glycosides in the absence of a promoter[208] or *N*'-glycopyranosylsulfonohydrazides donors for protecting group free synthesis of *O*-glycosides, glycosyl azides, and oxazolines.[209] However, there are only few examples of unprotected halide donors, which may be employed in the halide ion-mediated glycosylation.

In 2008 McLeod *et al.*[210] described the synthesis of the unprotected glucosyl fluoride. This reaction is shown in Scheme 62. The compound was stable towards column chromatography and later was subjected to the oxidation with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and sodium hypochlorite.



Scheme 62 Synthesis of the unprotected glucosyl fluoride.[210]

The only report on the formation and characterization of an unprotected glucosyl chloride comes from Williams and co-workers from 2014, shown in Scheme 63.[211]

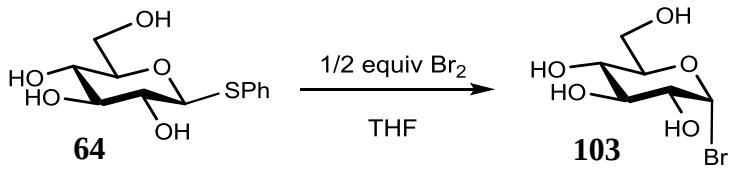


Scheme 63 Formation of unprotected glucosyl chloride for NMR studies.[211]

In the protocol proposed by Williams *et al.* the chloride was formed in situ from *N'*-glycosylsulfonohydrazides (GSHs) by adding NBS, Bu_4NCl and 2,6-lutidine. Subsequently, 20 equivalents of methanol were added. The reaction was performed in different deuterated solvents: DMF, CH_3CN, acetone, THF and CH_2Cl_2. NMR characterization showed the formation of the β-methyl glucoside in all of the solvents. The formation of an unprotected glucosyl bromide was also attempted in the same way as with the chloride (Bu_4NCl was exchanged for Bu_4NBr) and afterwards glycosylation with methanol was performed. However, the methyl glucoside was not formed and NMR studies did not confirm the formation of the bromide donor[211].

Another reference to the formation of unprotected glucosyl bromide comes from Muramatsu.[192] An unprotected bromide acceptor was supposed to be prepared from 2,3,4,6–tetra-*O*-acetyl-α-D-glucopyranosyl bromide according to McLeod's procedure, described above in Scheme 62. There is no NMR confirmation to the formation of the bromide and subsequent reaction gave less than 1 % yield. Experience from the Madsen group and others have shown that glycosylation with a free hydroxyl group in the donor at position 2 gives high 1,2-*trans* selectivity. [24, 65]

Our idea for forming unprotected glucosyl bromide **103** is depicted in Scheme 64.



Scheme 64 Proposed way for synthesis of unprotected bromide donor.

Problems, however, have been encountered already at the beginning, because the unprotected thioglycoside **64** was not soluble in common solvents like CH_2Cl_2, DCE or DME. The only solvent, in which the acceptor was soluble was THF. Thioglycoside **64** was dissolved in THF and then bromine was added. The reaction turned yellow and then a white precipitate was formed. TLC showed that there was no more starting material in the reaction mixture but all attempts to make NMR characterization failed, because it was impossible to dissolve the precipitate.
The decision to use deuterated THF was then made and the reaction was run in the NMR tube. To 20 mg of the thioglycoside acceptor in the NMR tube, 5 ml of deuterated THF was added. When the acceptor was dissolved, 2 µl of bromine was added and the NMR was recorded. It was impossible to confirm the formation of the bromide donor and the only observed compound was **64**, which is why we decided not to perform any further studies with this reaction.

The literature shows that employment of an unprotected glucosyl chloride gives moderate stereoselectivity in the reaction with a large excess of methanol which requires about 2h at 0 °C.[211] Therefore unprotected glucosyl bromide would be a desired species, due to the potential high reactivity that could improve those parameters. However, the unsuccessful attempt at synthesizing the glucosyl bromide could indicate that this donor might be too reactive to take part in the glycosylation and the chance for self-condensation would be very high. Moreover, restricted solubility of the unprotected species would also limit the probable glycosylation conditions.

3.2 Koenigs-Knorr glycosylations

3.2.1 Regioselective Glycosylation with Phenylboronic acid as a Temporary Masking Group

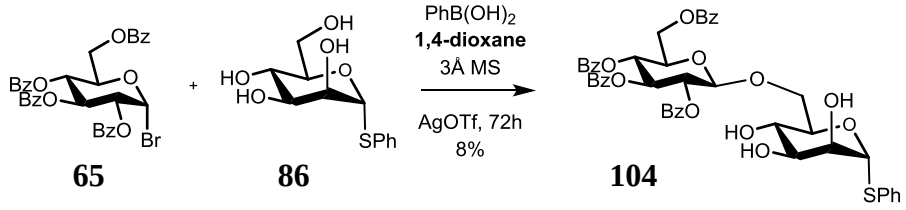
Despite being well established, the stannylene-mediated method generally requires an additional synthetic step to install the activating stannylene group. In addition, the majority of the protocols use stoichiometric amounts of toxic organotin species, which creates a limitation. On the other hand, nontoxic organoboron compouds could be used in an alternative procedure that works by masking the corresponding hydroxyl groups.[177] In this way, boronic acid derivatives can function as a temporary protecting group and the glycosyl donor can attack the most reactive free hydroxyl group leading to a regioselective glycosylation.[178]

As mentioned above, the mannose acceptor **86** that is shown in Scheme 55, was earlier employed in the glycosylation with phenylboronic acid, but the boronic ester of the acceptor was not soluble in DME.[65] Results of the investigation on the solubility of that complex are presented in Table 9.

Table 9 Solvent screening for solubility of the boronate complex of **86**.

Entry	Solvent	Solubility of the boronate complex
1	DME	insoluble
2	1,2-DCE	insoluble
3	CH_2Cl_2	insoluble
4	1,4-dioxane	soluble
5	DME 1,4-dioxane	insoluble
6	1,2-DCE 1,4-dioxane	insoluble
7	DME DMSO	insoluble
8	DME DMF	insoluble
9	Diglyme	insoluble

In DME, DCE, CH_2Cl_2 and diglyme (Entries 1, 2, 3 and 9) the boronate complex was not soluble and precipitated from the solution. Further solvent investigation showed that in 1,4-dioxane, the boronate complex was soluble (Entry 4). The solution was syringed into a solution of the bromide donor **65** and the glycosylation was performed. After 72 hours, phenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-α-D-mannopyranoside (**104**) was isolated, as shown in Scheme 65.



65 **86** **104**

Scheme 65 Glycosylation with mannosyl acceptor.

In addition to the disaccharide, the unreacted mannosyl acceptor and the hydrolyzed donor were isolated. The regioselectivity of the coupling reaction was confirmed by

HMBC analysis and a correlation between the H-6 in the acceptor and the C-1' at the donor anomeric carbon was observed. Furthermore, the anomeric configuration of the disaccharide was determined from the size of $^{3}J_{H}$ coupling constant between H-1' and H-2' and 7.8 Hz corresponds with the β-anomer. The isolated product was a 1,6-linked disaccharide and this result could be explained on the ground of boronate formation in the α-D-mannoside. As depicted in Figure 13, there are two places in mannose, where boronate esters could be formed.

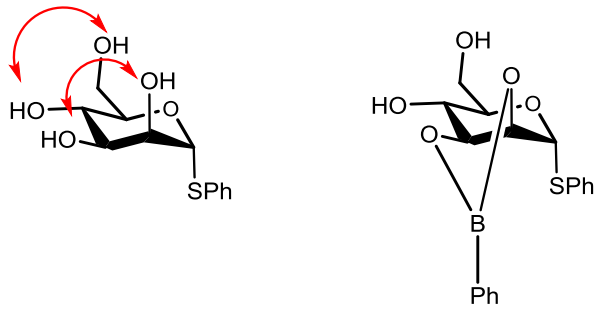


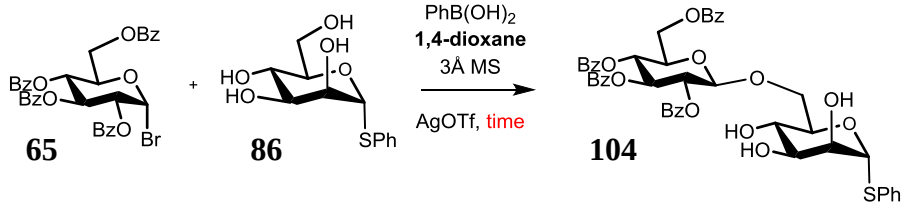
Figure 13 Possible formation of boronate esters in mannose.

In the mentioned reaction, the 2,3-boronate was most likely formed, as shown in Figure 13, allowing the glycosylation to take place at the free hydroxyl groups. In this case, the reaction took place on the primary hydroxyl group, which is more reactive and less sterically hindered, than the hydroxyl group at the 4 position.
Returning to the solvent screening, it is deemed that solvents like dioxane or THF can be too acid labile to use in the glycosylation with silver triflate.[212] For that reason, we wanted to investigate if dioxane could be used as an additive in the formation of the boronate complex. Dioxane has been added to DME (Entry 5) and to DCE (Entry 6), but the boronate complex was again insoluble. DMSO (Entry 7) and DMF (Entry 8) have also been tried as additives but without success.

Running the reaction according to the procedure developed earlier in the group[65] assumed formation of the boronate complex by stirring the unprotected glycosyl acceptor with the boronic acid and molecular sieves overnight. Then an aliquot of the boronate complex in solution was transferred to the bromide donor and the mixture was stirred overnight again with molecular sieves. Following this, the reaction was cooled to 0 °C and AgOTf was added and the mixture stirred for 3 hours. Then, CH_2Cl_2, MeOH and Amberlite IRA 743 were added and the mixture

was stirred overnight. In Table 10 the results of the optimization of the glycosylations are shown.

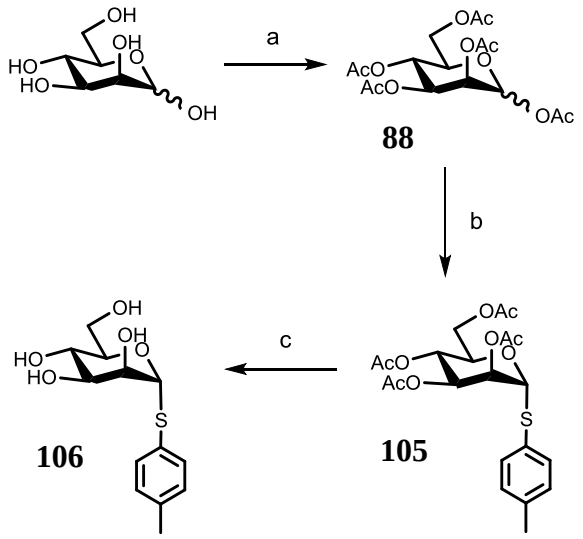
Table 10 Screening of the glycosylation conditions.



Entry	Temperature (°C)	Time (h)	Yield of disaccharide (%)
1	r.t – 0 °C –r.t	72	8
2	r.t	48	7
3	r.t – 0 °C	48	9
4	r.t	24	7

First, the reaction was carried out according to the original procedure and that led to the disaccharide product in 8% yield (Entry 1). Shorter reaction time was investigated and running the whole reaction at room temperature was tried (Entries 2 and 4) but that also gave an unsatisfactory yield. The last conditions studied (Entry 3) was running the reaction over 48 hours and keeping it at 0 °C for 3 hours after addition of AgOTf, then quenching and work up the same day. The reaction yielded 9 % and at this point the optimization was discontinued.

Facing the solubility problem of the mannose acceptor **86** in the optimal solvents like DME or DCE and being unable to obtain higher yields in 1,4-dioxane, the decision to modify the acceptor was made. The way of the alternative synthesis is shown in Scheme 66 and the synthesis was done according to a literature procedure.[181,198,213]



a: *iodine, Ac_2O (60%);* **b:** *4-Methylthiophenol, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (60%);* **c:** *Na in MeOH (quantitative)*

Scheme 66 Synthesis of the *p*-tolyl 1-thio-α-D-mannopyranoside.

Employing a methyl group in the *para* position of the thiophenol could give the new acceptor more solubility than with the parent thiophenol. Synthesis of the acceptor started from D-mannose, followed by acetylation in the presence of iodine and acetic anhydride. The reaction was finished after one hour and NMR characterization confirmed the formation of the acetylated mannose and the product was isolated in 60% yield. After a long drying process, the compound became a solid that was used in further reactions. Compound **88** was dissolved in CH_2Cl_2 and 4-methylbenzenethiol and boron trifluoride etherate were added to install the new group in the anomeric position to give **105**. The next step was Zemplén deacetylation, which led to the desired acceptor **106**.[181,198,213]

The formation of the boronate in DCE was performed with the newly synthesized mannosyl acceptor **106** and then subjected to the same glycosylation procedure, as shown in Scheme 65. Disappointingly, the reaction showed formation of the disaccharide in a 15% yield and formation of 1,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranose, 1,2,3,4,6-penta-*O*-benzoyl-D-glucopyranose and 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose in the reaction mixture. Generally, presence of such by-products is reduced, when the benzoyl protecting group is used in the glycosylation.

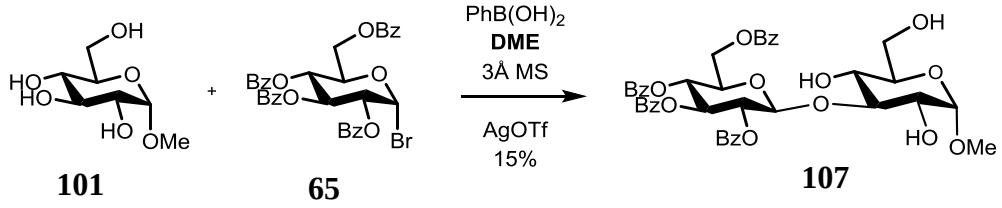
However, as our example and the study of Murakami *et al.*[214] showed, it cannot be fully avoided.

Formation of the boronate complex with phenylboronic acid leads to the formation of 1-2 equivalents of water. The use of dichlorophenylborane would eliminate that problem. Therefore, the boron source was changed from phenylboronic acid to dichlorophenylborane, both shown in Figure 14.

Figure 14 Structures of phenylboronic acid and dichlorophenylborane.

Next, the boronate complex was formed with dichlorophenylborane and mannosyl acceptor **106** and the glycosylation was then performed (Scheme 65). The reaction yield reached 35% and at that point, further investigation was not continued.

All the acceptors used in the procedure developed in Madsen's group were thioglycoside acceptors. Kaji and co-workers[179] obtained good results when using methyl hexopyranoside acceptors, based on galactose, fucose and rhamnose, but very poor results when a glucose acceptor was employed in the glycosylation. The decision was made to employ **101** in the procedure developed earlier in the Madsen's group[65] and the reaction is shown in Scheme 67.



Scheme 67 Glycosylation with methyl-α-D-glucoside.

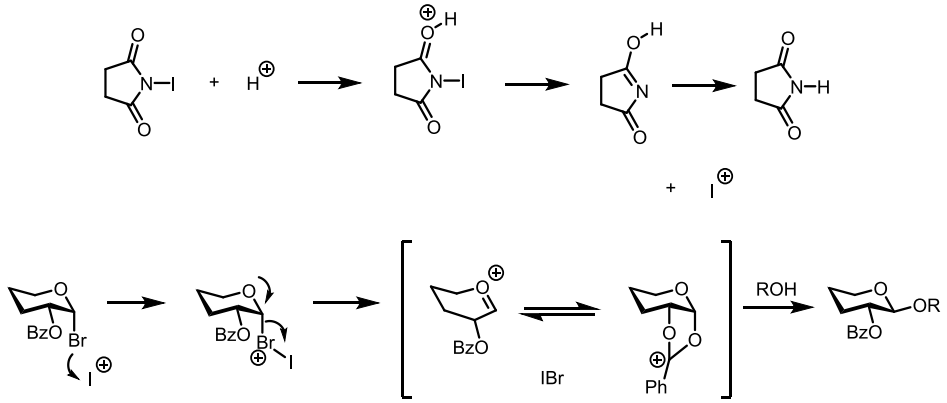
The (1→3)-linked disaccharide **107** was the only glycosylation product obtained, together with the orthoester, fully benzoylated glucose, and small amounts of the hydrolyzed donor. The result is an improvement of Kaji's experiment because there was no formation of another glycosylation product, i.e. the (1→2)-linked disaccharide. Nevertheless, the yield was comparable. Kaji obtained the (1→3)-linked product in a 18% yield and the product of glycosylation in our conditions was isolated in a 15% yield. The reaction was repeated with dichlorophenylborane but

the yield remained around 15% and at that point, further investigation was not continued.

3.2.2 Regioselective Glycosylation with Diarylborinic acid derivative

As mentioned above, Taylor and co-workers were successfully using diarylborinic derivatives for glycosylation or alkylation of monosaccharides protected at the 6 position and silver oxide was used as a promoter.[175,215]

Recently, in Robert Madsen's group, PhD student Gyrithe Lanz investigated NIS/CSA promoting system.[216] The proposed mechanism of the reaction is shown in Scheme 68.

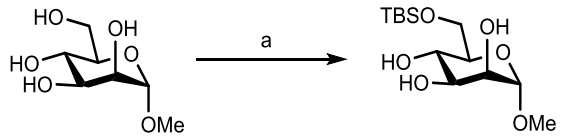


Scheme 68 Possible mechanism of NIS/CSA activation.

The mechanism of the glycosylation is expected to involve the iodonium ion, which acts as a halophile and that result in iodobromonium formation at the anomeric center. This is followed by fragmentation to give I-Br and a carbohydrate derived oxocarbenium ion.[216]

In the present work, we decided to apply the NIC/CSA system in the glycosylation of unprotected carbohydrates catalyzed by diphenylborinic acid 2-aminoethyl ester.

One of the acceptors widely used by Taylor is methyl mannoside with *t*-butyldimethylsilyl protection on the primary alcohol.[215] Synthesis of the compound is shown in Scheme 69, following Taylor's procedure.[215]

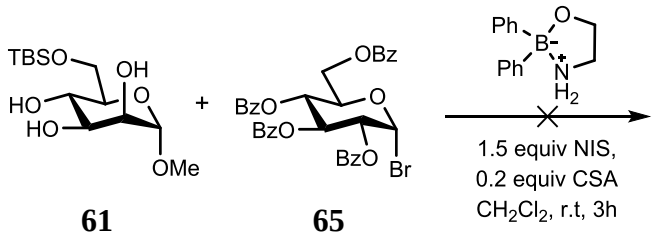


61

a: *TBSCl, pyridine (86%)*

Scheme 69 Synthesis of methyl 6-*O*-(*tert*-butyldimethylsilyl)-α-D-mannopyranoside.

The reaction gave only one product, protected at the 6 position, in a 86% yield. Acceptor **61** and the borinic ester were dissolved in CH_2Cl_2 at room temperature and then the bromide donor was added, as shown in Scheme 70. After stirring the mixture for 15 minutes, 1.5 equivalent of NIS and 0.2 equivalent of CSA were added and the reaction was monitored by TLC.



61 **65**

Scheme 70 Diphenyl borinic acid catalyzed glycosylation with methyl methyl 6-*O*-(*tert*-butyldimethylsilyl)-α-D-mannopyranoside.

Within 3 hours many new spots appeared on TLC. The reaction was worked up and subjected to column chromatography. The isolation and characterization by NMR showed no disaccharide formation, but instead products of deprotection and migration of the *t*-butyldimethylsilyl group were observed. In fact, *t*-butyldimethylsilyl ethers can migrate under acidic conditions[177] and deprotection of this group can be performed with a catalytic amount of *N*-iodosuccinimide.[217]

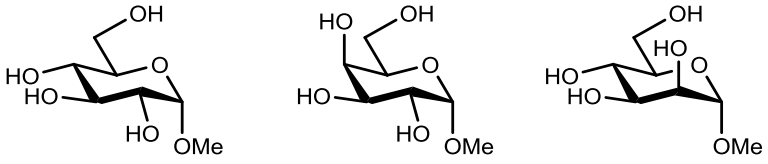
Having available other compounds used as acceptors by Taylor *et al.*[218] namely 1,6-anhydro-β-D-mannopyranose and methyl β-L-arabinopyranoside (**108**), which are shown in Figure 15, we subjected them to the glycosylation with NIS/CSA promoting system.

108

Figure 15 Structures of D-mannosan and methyl β-L-arabinopyranoside.

Unfortunately, the solubility of 1,6-anhydro-β-D-mannopyranose and **108** turned out to be an essential problem for the glycosylation, as both acceptors were not soluble in dichloromethane at room temperature. The glycosylation led to isolation of unreacted acceptor and unreacted and decomposed donor.

Expecting that glucose, galactose and mannose will work under the NIS/CSA conditions, methyl α-derivatives of those acceptors (**101**, **109** and **110**) have been selected for further studies, as presented in Scheme 71.



101 **109** **110**

Scheme 71 Acceptors used for benzoylation.

Knowing that the *t*-butyldimethylsilyl group at the 6 position is too unstable under the NIS/CSA conditions, a more stable benzoyl group was selected as a protecting group for the primary position of compounds **101**, **109** and **110**. The most reactive hydroxyl group towards benzoylation in the methyl α-D-glycopyranosides should be the primary alcohol. From secondary alcohols the most reactive in glucose is 2-OH and then 3-OH, in mannose it is 3-OH and then 2-OH. In galactose, 2-OH and 3-OH are equally reactive. The least reactive position in all three monosaccharides is the 4-OH position.[219] Different conditions for benzoylation has been investigated and they are presented in Table 11.

Table 11 Conditions for regioselective benzoylation of **101**, **109** and **110** and products.

Entry	Conditions	Product
1	TBTU, DIPEA, Benzoic acid[220]	mixture of di- and tri-benzoylated
2	Benzoic anhydride, I_2, dioxane[221]	mixture of di- and tri-benzoylated
3	DEAD, Benzoic acid, Ph_3P[222]	Bz at 6-OH in glucose
4	BzCl pyridine, -40 °C[223]	Bz at 3-OH in mannose
5	BzCl, DMAP pyridine[224]	mixture of di- and tri-benzoylated

Standard conditions (Entry 4) with 1 equivalent of BzCl in pyridine at -40 °C gave the monobenzoylation only in case of methyl α-D-mannopyranoside (**110**) and the product of this reaction was methyl 3-*O*-benzoyl-α-D-mannopyranoside, isolated in a 70% yield. In the case of methyl α-D-gluco- and galactopyranosides, benzoylation led to different di- and tribenzoylated products, which were not characterized in further detail.

In the literature there are a few examples on regioselective 6-benzoylation. Peptide coupling agents like TBTU together with diisopropylethylamine can be used for regioselective esterification of the 6 position and they are shown in Figure 16.

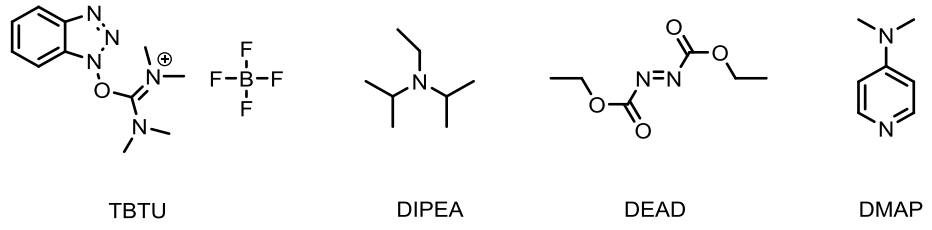
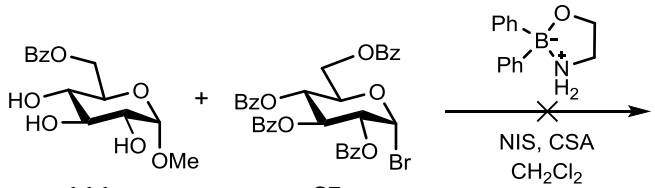


Figure 16 Structures of TBTU, DIPEA, DEAD and DMAP.

Grindley *et al.*[220] observed that this combination of reagents is not reacting with secondary alcohols. However, we obtained a mixture of di- and tri-benzoylated products with all monosaccharides (Entry 1).

While using the Mitsunobu reaction (Entry 3), the monobenzoylated product was formed only in the case of **101** to give methyl 6-*O*-benzoyl-α-D-glucopyranoside. Two other procedures were also investigated (Entries 2 and 5) but the outcome of the reaction was a mixture of di- and tri-benzoylated products.

The methyl 6-*O*-benzoyl-α-D-glucopyranoside (**111**) was employed in the glycosylation shown in Scheme 72.

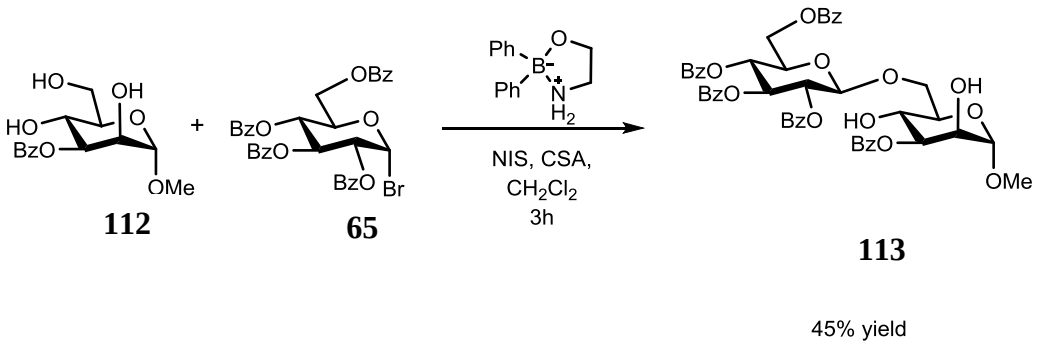


111 **65**

Scheme 72 Diphenyl borinic acid catalyzed glycosylation with methyl 6-*O*-benzoyl-α-D-glucopyranoside.

The acceptor **111** was not an optimal choice for the glycosylation with the boronate catalyst because this catalyst does not promote reaction on the secondary hydroxyl groups in carbohydrates lacking a *cis*-1,2-diol motif such as xylose and glucose. In fact, the reaction led to unreacted bromide donor, hydrolyzed donor and unreacted acceptor.

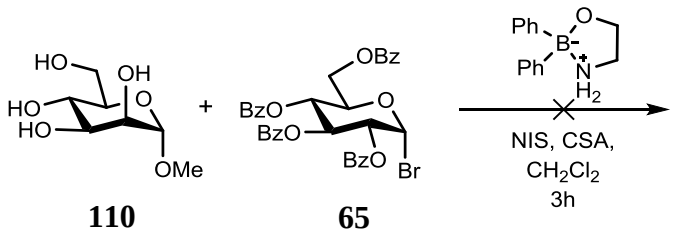
Another synthesized acceptor, methyl 3-*O*-benzoyl-α-D-mannopyranoside (**112**) was not used in the Taylor work but we nevertheless employed it in the coupling, as shown in Scheme 73.



112 **65** **113**

Scheme 73 Diphenyl borinic acid catalyzed glycosylation with methyl 3-*O*-benzoyl-α-D-mannopyranoside.

The product of the reaction was (1→6)-linked disaccharide **113** in a 45% yield but it was probable that this reaction could work without a borinic catalyst. The reaction was repeated without diphenylborinic acid 2-aminoethyl ester and the (1→6)-linked disaccharide was formed, but only in a 15% yield. This result could indicate that the borinic ester catalyzes the reaction, since both reactions were run under the same conditions over 3 hours, with the latter just without the catalyst. At last, the reaction with completely unprotected mannosyl acceptor was performed, as showed in Scheme 74.



110 **65**

Scheme 74 Example of glycosylation with fully unprotected acceptor.

This time, a complex mixture of products was observed according to TLC and this result can be explained by the relative affinity of borinates for diols that in most carbohydrates have the following order: *cis*-1,2-diol > 1,3-diol >> *trans*-1,2-diol. That could explain the formation of borinates in the 2,3- and the 4,6-position in the unprotected mannose and therefore formation of at least two coupling products. In case of 3-benzoyl protected mannose the *cis*-1,2-diol was unavailable to form a borinate ester and as a result borinate form the 1,3-diol could be formed and catalyze the reaction.[225]

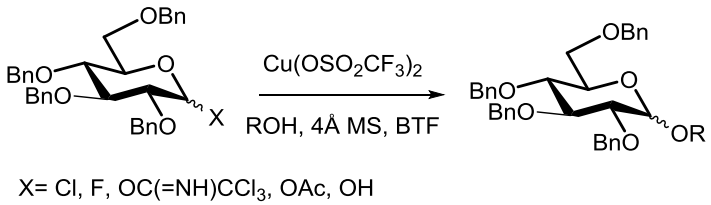
Based on one positive result from the coupling of the borinate-mediated acceptor with the benzoylated bromide donor, it is impossible to establish if NIS/CSA really promotes the glycosylation. So far, no examples of NIS/acid-promoted glycosylation with unprotected carbohydrates have been found in the literature.

3.2.3 Glycosylation with copper salts as promoters

There are not many examples of using copper salts as promoters in the glycosylation with halide donors. One of the first examples is from 1971, where

Bernstein and Conrow described attempted Koenigs-Knorr glycosylation with various metal salts, including copper (II) carbonate ($CuCO_3$) and copper (II) hydroxide ($Cu(OH)_2$). However, in the case of copper (II) salts glycosylation products have not been observed.[226]

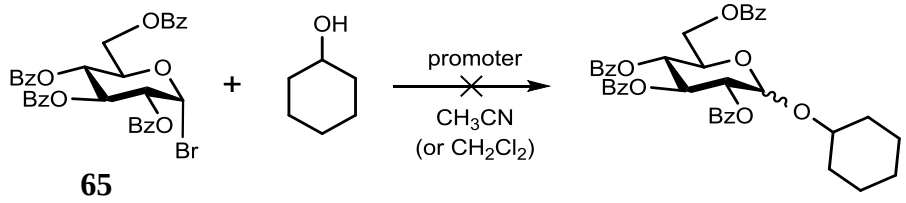
In 2002 Yamada and Hayashi described a glycosylation promoted by copper (II) trifluoromethanesulfonate in benzotrifluoride (BTF). The promoter was found to activate five kinds of glucosyl donors, as shown in Scheme 75.[227]



Scheme 75 Example of glycosylation with copper (II) trifluoromethanesulfonate used as a promoter. [227]

Cyclohexylmethanol was used as an acceptor and diethyl ether, acetonitrile, 1,2-DCE and BTF were tested as solvents for the glycosylation. The best yields and selectivity were obtained, when using BTF. The reaction was applied to more hindered alcohol acceptors: tertiary 2-methyl-2-propanol, secondary cholesterol and the sugar methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside. All these reactions were conducted in BTF and gave moderate to good both yields and selectivities.[227]

Copper salts could be a good alternative to silver salts, which are relatively expensive promoters. Especially, copper (I) could form the insoluble copper(I)bromide that could trigger the coupling reaction. 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**65**) and cyclohexanol were used in our group as a model system to test NIS/CSA as a promoter.[216] The decision was made to use the same model system to try copper salts as promoters in the glycosylation, as presented in Scheme 76.



Scheme 76 Model reaction for trying copper salts as a promoter in the glycosylation.

Six different copper compounds with copper in +1 and +2 oxidation states were tested, as presented in Table 12.

Table 12 Screening various copper salts as promoters in the glycosylation.

Entry	Promoter	Equivalent	Temperature	Product
1	Cu_2O	5	r.t	-
2	CuI	1,5	r.t	-
3	CuO	5	r.t	-
4	$Cu(OTf)_2$	1,5	r.t	-
5	$Cu(acac)_2$	1,5	r.t	-
6	$Cu(ethylacetoacetate)_2$	1,5	r.t	-

The reaction was running for 4 days with continuous TLC monitoring. In the case of copper (I) salts (Entry 1 and 2) dichloromethane was used as a solvent because possibly formed copper (I) bromide is soluble in acetonitrile. During the 4 days of conducting the reaction no precipitation of the copper (I) bromide was observed. NMR characterization showed both unreacted donor and acceptor presence after that time.

Copper oxides (Entry 1 and 3) have been used in excess because of their poor solubility in the reaction mixture and the rest of the salts with 1.5 equivalent. Unfortunately, no coupling product was observed in any of the reactions. In the case of copper (II) triflate (Entry 4) hydrolyzed donor was the major product of the reaction. The possible explanation could be that copper (II) triflate, a very hygroscopic species, absorbs water and hydrolyzes the donor.

Despite the previous indication that copper salts can take part in the regioselective acylation, alkylation[117, 153, 228] and glycosylation[226, 227] the investigation presented above did not lead to any coupling products. One of the reasons could be the poor solubility of copper salts in the reaction mixture that prevented activation of the glycosyl donor.

4 Conclusion

The role of tin was investigated in the regioselective glycosylation of 2,3,4,6-unprotected hexopyranosides with perbenzylated glycosyl bromide donors. Reactions with phenyl 1-thio-β-glucopyranoside and phenyl 1-thio-β-galactopyranoside with glucosyl and galactosyl bromide donors afforded exclusively the corresponding α(1→6)-linked disaccharides in decent yields. The coupling was highly dependent on the solubility of the acceptors with dibutyltin oxide in dichloromethane and it was successful in case of glucose and galactose, while no coupling occurred with mannose. The same behavior was observed for donors, where no conversion took place with mannosyl bromide. In addition, Ph_2SnCl_2, Bu_2SnCl_2, Me_2SnCl_2 and Me_2SnO were tested in the glycosylation. These experiments also led to α(1→6)-linked products but with very poor yields.

The role of organoboron derivatives was studied for the Koenigs-Knorr glycosylation. In all experiments with boron, perbenzoylated α-D-glucopyranosyl bromide was used as a donor.

Previous investigation showed that glycosylation of unprotected acceptors by the use of transient masking with a boronic acid leads to (1→3)-linked disaccharides.[65] In this work, mannosyl acceptors have been investigated but because of their poor solubility, the yields of the obtained disaccharides were not higher than 35%.

The diphenylborinic acid catalyzed glycosylation has been investigated before with Ag_2O[218] and AgOTf[229] as the promoters. Here, the glycosylation was conducted with the NIS/CSA promoter system[216]. Yet again poor solubility of the acceptors, namely D-mannosan and methyl L-arabinopyranoside led to no coupling products in the glycosylation. The only positive result was achieved when methyl 3-*O*-benzoyl-α-D-mannopyranoside (**112**) was used as an acceptor. The glycosylation with borinic catalyst and **112** led to the (1→6)-linked disaccharide in a 45% yield. However, glycosylation under the same conditions but without the catalyst afforded the (1→6)-linked product in a 15% yield.

The investigation presented in this thesis shows that tin- and boron-mediated glycosylation with unprotected carbohydrates is successful, when the components of the reaction mixture are soluble in a given solvent. Insolubility of the unprotected acceptors puts a considerable limitation on a developed method and therefore further research on that matter would be valuable for the field.

5 Experimental section

General remarks: All reactions were performed under an argon atmosphere. Molecular sieves (MS) were flame-dried before use. Dichloromethane and tetrahydrofuran were taken from Pure Solve Solvent Purification System. Tetrabutylammonium bromide (TBAB) was recrystallized from ethyl acetate and dried at 60 °C under high vacuum. TLC was performed on aluminum plates coated with silica gel 60. The plates were visualized with UV light or developed by dipping into a solution of cerium (IV) sulfate (2.5 g) and ammonium molybdate (6.25g) in sulfuric acid (10%; 250 mL) followed by heating. Column chromatography was carried out on a HPLC grade solvents on silica gel 60 (230-400 mesh). NMR spectra were recorded with Bruker Ascend instrument with a Prodigy cryoprobe. Chemical shifts were calibrated to the residual solvent signal in $CDCl_3$ (δ_H = 7.26 ppm, δ_C = 77.16 ppm), CD_3OD, DMSO and TMS. Assignment of ^1H and ^{13}C resonances were based on COSY, HSQC, and HMBC experiments. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. IR spectra were recorded with a Bruker Alpha P FTIR instrument. High resolution mass spectra were recorded on an Agilent 1100 LC system which was coupled to a Mircromass LCT orthogonal time-off light mass spectrometer.

General procedure for substitution with thiophenol[180]

Under an argon atmosphere pentaacetylated glucose/mannose/galactose (130 mmol) was dissolved in anhydrous CH_2Cl_2 (250 mL) and $BF_3{\cdot}Et_2O$ (238 mmol) was added. At 0 °C PhSH (292 mmol) was added dropwise and reaction mixture was allowed to warm to room temperature. After completion saturated $NaHCO_3$ solution (350 mL) was added until all boron trifluoride was hydrolyzed. The phases were separated and the organic phase was washed with water and saturated $NaHCO_3$ several times. The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* and crystallized from Et_2O to give the product as white crystals.

General procedure for Zemplén deacetylation[181]

An acetylated compound (0.129 mmol) was dissolved in MeOH (100 mL) and Na (43.4 mmol) in MeOH (150 mL) was added to the reaction. The mixture was stirred for 3 h and a portion of dry ice was added to neutralize the mixture. After removal

of the solvent *in vacuo*, the crude product was purified by flash chromatography/crystallization.

General procedure for bromination with oxalyl bromide[146]

Oxalyl bromide (1.3 mmol) was added dropwise to a solution of the starting material (1 mmol) in anhydrous dichloromethane (10 mL). The reaction was stirred until disappearance of the starting material (TLC, EtOAc:Heptane, 2:5). Then the reaction mixture was diluted with dichloromethane, washed with water and brine. The dichloromethane solution was dried with Na_2SO_4 and evaporated. The product was purified by column chromatography (EtOAc:Heptane=2:5) to obtain the product as a syrup.

General procedure for chlorination with oxalyl chloride[146]

Oxalyl chloride (1.3 mmol) was added dropwise to a solution of a starting material (1 mmol) in anhydrous dichloromethane (10 mL). The reaction was stirred until disappearance of the starting material (TLC, EtOAc:Heptane, 2:5). Then reaction mixture was diluted with dichloromethane, washed with water and brine. The dichloromethane solution was dried with Na_2SO_4 and evaporated. The product was purified by column chromatography (EtOAc:Heptane=2:5) to obtain the product as a syrup.

General procedure for benzylation[182]

Unprotected phenyl 1-thio-β-D-glycopyranoside (14.7 mmol) was dissolved in dry DMF (40 mL) and then TBAI (1.94 mmol) and BnBr (88.6 mmol) were added. A total of 2.34 g of NaH (4.25 g 60% NaH-suspension in oil) was transferred to the flask and a $CaCl_2$-tube was applied. After completion, the reaction mixture was quenched with glacial acetic acid until pH was neutral. Then 50 ml of water was added and the mixture was cooled to 0 °C. White crystals were filtered off and recrystallized from EtOH and dried under high vacuum.

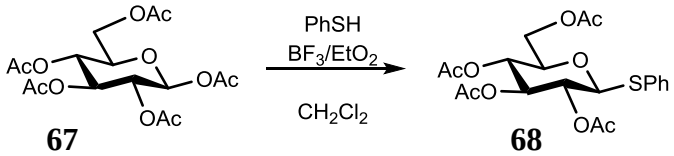
General procedure for cleavage of thiophenol[230]

The thioglycoside (3.16 mmol) was dissolved in a mixture of acetone/water (9:1 v/v) and NBS (6.74 mmol) was added at rt. The mixture was stirred until completion, then diluted with water and extracted with ether several times. Combined organic phases were washed with saturated $NaHCO_3$ and dried over Na_2SO_4. After removal

of the solvent in vacuo, the crude product was purified by column chromatography (Heptane: EtOAc= 5:2).

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (68)

Synthesized according to the general procedure for thiophenol substitution in 82% yield. NMR data in accordance with the literature values.[231]

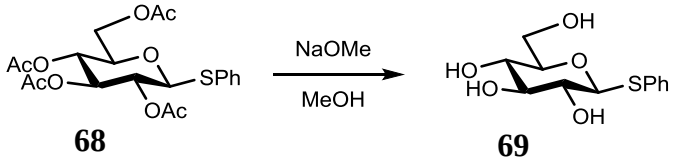


67 **68**

^{1}H NMR (400 MHz, CD_3Cl): δ = 7.49 – 7.42 (m, 2H, H_{Ar}), 7.33 – 7.24 (m, 3H, H_{Ar}), 5.19 (t, 1H, *J* = 9.2 Hz, H-3), 5.02 (dd, 1H, *J* = 9.5 Hz, *J* = 9.6 Hz, H-4), 4.93 (dd, 1H, *J* = 9.1 Hz, *J* = 9.8 Hz, H-2), 4.70 (d, 1H, *J* = 9.9 Hz, H-1), 4.24 (dd, 1H, *J* = 4.6 Hz, *J* = 12.1 Hz, H-6b), 4.14 (dd, 1H, *J* = 2.7, *J* = 12.3 Hz, H-6a), 3.73 (ddd, 1H, *J* = 2.7 Hz, *J* = 4.8 Hz, *J* = 10.1 Hz, H-5), 2.05 (s, 3H, COC*H*$_3$), 2.04 (s, 3H, COC*H*$_3$), 1.95 (s, 3H, COC*H*$_3$), 1.99 (s, 3H, COC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.5, 170.1, 169.4, 169.1 (4x $COCH_3$), 133.2, 131.2, 128.6, 128.1, 85.4 (C1), 75.2 (C5), 73.5 (C3), 69.5 (C2), 67.9 (C4), 61.8 (C6), 20.5, 20.5, 20.3, 20.3 (4x$COCH_3$) ppm.

Phenyl 1-thio-β-D-glucopyranoside (69)

Synthesized according to the general procedure for Zemplén deacetylation. NMR data in accordance with the literature values.[231]

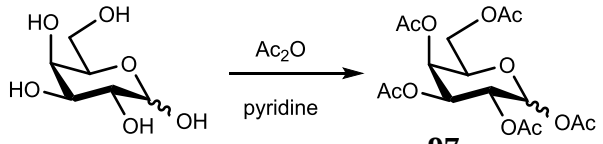


68 **69**

^{1}H NMR (400 MHz, CD_3OD): δ = 7.56-7.28 (m, 5 H, H_{Ar}), 4.58 (d, 1H, *J* = 9.7 Hz, H-1), 3.66 – 3.62 (m, 1H, H-6), 3.47 – 3.45 (m, 1H, H-6), 3.27-3.19 (m, 4H, H-2,3,4,5) ppm. ^{13}C NMR (CD_3OD): δ = 134.6, 129.1, 128.7, 126.1, 87.2 (C1), 80.6 (C2), 78.3 (C5), 72.1 (C3), 69.3 (C4), 61.2 (C6) ppm.

Penta-*O*-acetyl-D-galactopyranose (97)

Synthesized according to the general procedure for acetylation in 82% yield. NMR data in accordance with the literature values.[232]

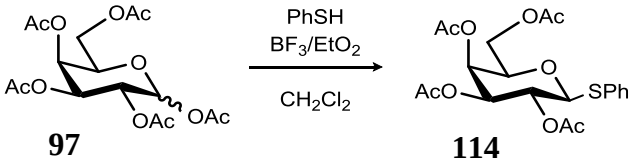


97

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.32 (s, 1H, H-1α), 5.59 (d, 1H, *J* = 8.4 Hz, H-1β), 5.41 (s, 1H, H-4α), 5.38 (s, 1H, H-4β), 5.35-5.28 (m, 3H, H-2α, H-2β, H-3α), 5.06 (dd, 1H, *J* = 3.1 Hz, *J* = 10.4 Hz, H-3β), 4.32−4.28 (m, 2H, H−6aβ, H−5α), 4.11−4.05 (m, 4H, H-6abα, H-6bβ, H-5β), 2.13 (s, 9H, 3 COC*H*$_3$α), 2.13 (s, 3H, COC*H*$_3$β), 2.02 (s, 6H, 2xCOC*H*$_3$α), 2.01 (s, 6H, 2xCOC*H*$_3$β), 2.00 (s, 6H, 2xCOC*H*$_3$β) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.0, 169.1, 168.7, 168.3, 92.3 (C1β), 90.1 (C1α), 71.7 (Cβ), 71.0 (Cβ), 69.0 (Cα), 68.1 (Cβ), 67.4 (2Cα), 67.0 (Cβ), 66.5 (Cα), 61.1 (Cα,β), 21.0, 21.0, 20.8, 20.6 ppm.

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (114)

Synthesized according to the general procedure for thiophenol substitution in 58% yield. NMR data in accordance with the literature values.[233]

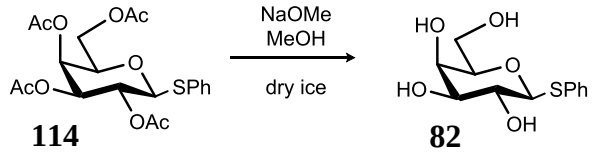


97 **114**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45-7.18 (m, 5H, H_{Ar}), 5.33 (d, 1H, *J* = 3.1 Hz, H-4), 5.14 (t, 1H, *J* = 10.2 Hz, H-2), 5.00 (dd, 1H, *J* = 3.2 Hz, *J* = 10.1 Hz, H-3), 4.62 (d, 1H, *J* = 10.2 Hz, H-1), 4.11 (dd, 1H, *J* = 7.2 Hz, *J* = 11.6 Hz, H-6a), 4.03 (dd, 1H, *J* = 6.2 Hz, *J* = 11.5 Hz, H-6b), 3.88 (t, 1H, *J* = 6.6 Hz, H-5), 2.03 (s, 3H, COC*H*$_3$), 2.01 (s, 3H, COC*H*$_3$), 1.96 (s, 3H, COC*H*$_3$), 1.90 (s, 3H, COC*H*$_3$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.1, 169.9, 169.8, 169.3, 132.1, 128.3, 127.4, 127.3, 86.0, 74.3, 71.4, 71.2, 66.8, 61.2, 20.3, 20.1, 20.0, 20.0 ppm.

Phenyl 1-thio-β-D-galactopyranoside (82)

Synthesized according to the general procedure for Zemplén deacetylation. NMR data in accordance with the literature values.[180]

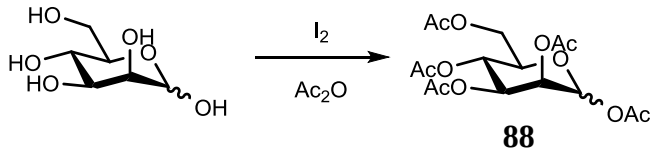


114 **82**

^{1}H NMR (400 MHz, CD_3OD): δ = 7.55-7.32 (m, 5H, H_{Ar}), 4.72 (d, 1H, *J* = 9.6 Hz, H-1), 3.92 (d, 1H, *J* = 3.2 Hz), 3.76–3.59 (m, 5H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ=133.0, 131.2, 129.4, 129.1, 88.1 (C1), 79.1, 74.2, 69.4, 68.7, 61.1 ppm.

Penta-*O*-acetyl-D-mannopyranose (88)[221]

D-mannose was suspended in acetic anhydride (5 ml/g of sugar) and stirred. Iodine (50 mg/g sugar) was added and the stirring was continued until TLC showed the reaction to be complete (30 minutes). The reaction mixture was poured into ice-cold dilute sodium thiosulfate solution with stirring. The mixture was diluted with CH_2Cl_2 and was washed successively with dilute aqueous sodium thiosulfate and aqueous sodium carbonate solutions. The organic layer was then dried (Na_2SO_4) and concentrated to give the product, as a brownish slurry in 60% yield. NMR data in accordance with the literature values.[234]



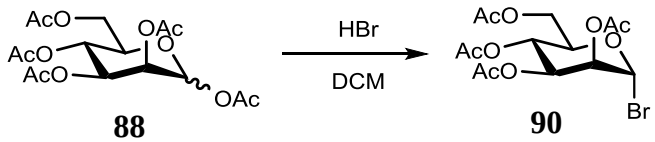
88

^{1}H NMR (400 MHz, $CDCl_3$): α/β = 1/3; α: δ = 5.79 (d, 1H, *J* = 1.2 Hz, H-1), 5.49 (dd, 1H, *J* = 1.4 Hz, *J* = 3.0 Hz, H-2), 5.30 – 5.26 (m, 1H, H-4), 5.02 (dd, 1H, *J* = 3.2 Hz, *J* = 10.1 Hz, H-3), 4.40 (dd, 1H, *J* = 4.6 Hz, *J* = 12.2 Hz, H-6a), 4.15 (dd, 1H, *J* = 2.4 Hz, H-6b), 3.81 (ddd, 1H, *J* = 2.4 Hz, *J* = 4.6 Hz, *J* = 10.0 Hz, H-5), 2.15 (s, 3H, COC*H*$_3$), 2.09 (s, 3H, COC*H*$_3$), 2.02 (s, 3H, COC*H*$_3$), 1.98 (s, 3H, COC*H*$_3$), 1.93 (s, 3H, COC*H*$_3$); β: δ = 6.01 (d, 1H, J = 1.6 Hz, H-1), 5.35 – 5.26 (m, 3H, H-3, H-4, H-2), 4.20 – 4.18 (m, 1H, H-6a), 4.02 – 3.99 (m, 2H, H-6b, H-5), 2.15 (s, 3H, COC*H*$_3$), 2.10 (s, 3H, COC*H*$_3$), 2.03 (s, 3H, COC*H*$_3$), 1.98 (s, 3H, COC*H*$_3$), 1.93 (s,

3H, COC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 170.3, 169.8, 169.7, 169.4, 169.4, 169.3, 169.2, 168.1, 167.7 (C=O), 90.3 (C1α), 90.2 (C1β), 72.8 (C5β), 70.4 (C5α), 68.6 (C3α), 68.1, 67.9 (C2α, C2β), 65.4, 65.3 (C4α, C4β), 61.8 (C6α, C6β), 20.6, 20.5, 20.5, 20.4, 20.44, 20.3, 20.3, 20.3, 20.2, 20.2 ppm.

2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (90)[198]

1,2,3,4,6-Penta-*O*-acetyl-mannopyranose (12.8 mmol) was dissolved in CH_2Cl_2 (60 mL). To this, hydrogen bromide (33 % in acetic acid, 75 mL) was added and the reaction mixture was stirred under argon at rt. After 2 hours, TLC (ethyl acetate/hexane; 1:1) indicated the formation of product with complete consumption of the starting material. The reaction mixture was partitioned between CH_2Cl_2 (100 mL) and ice water (100 mL) and the aqueous layer was re-extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were washed with sodium hydrogen carbonate (750 mL of a saturated aqueous solution) until pH 8 was obtained, washed with brine (250 mL), dried over $MgSO_4$, filtered and evaporated in vacuo to afford 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide as a pale yellow oil in 90% yield. NMR data in accordance with the literature values.[234]



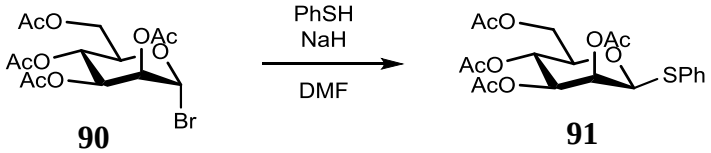
88 **90**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.23 (s_{br}, 1H, H-1), 5.65 (dd, 1H, *J* = 3.4 Hz, *J* = 10.1 Hz, H-3), 5.38 – 5.36 (m, 1H, H-2), 5.30 (t, 1H, *J* = 10.2 Hz, H-4), 4.27 (dd, 1H, *J* = 4.9 Hz, *J* = 12.5 Hz, H-6a), 4.16 – 4.14 (m, 1H, H-5), 4.07 (dd, 1H, *J* = 2.5 Hz, *J* = 12.5 Hz, H-6b), 2.18 (s, 3H, COC*H*$_3$), 2.11 (s, 3H, COC*H*$_3$), 2.08 (s, 3H, COC*H*$_3$), 2.01 (s, 3H, COC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 169.6, 169.5, 169.4, 82.9, 72.5, 72.1, 68.0, 65.3, 61.3, 20.7, 20.6, 20.6, 20.5 ppm.

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-mannopyranoside (91)[198]

Sodium hydride (40 mmol) was added gradually at room temperature under argon to a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (10 mmol) and thiophenol (40 mmol) in DMF (50 mL). The mixture was stirred for 30 minutes at room temperature until the hydrogen evolution had stopped, then poured into ice-cold water (1 L) and extracted three times with EtOAc. The extract was washed with

0.1 M aqueous hydrochloric acid, then water until neutral, dried with $MgSO_4$ and concentrated to give the product as a syrup in 85% yield. NMR data in accordance with the literature values.[198]

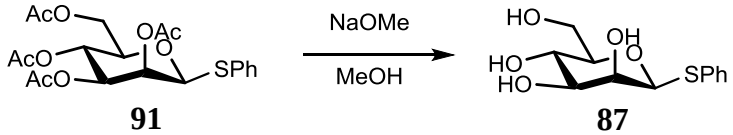


90 **91**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 - 7.08 (m, 5H, H_{Ar}), 5.60 (dd, 1H, *J* = 1.3 Hz, *J* = 3.5 Hz, H-2), 5.21 (t, 1H, *J* = 10.1 Hz, H-4), 4.98 – 4.96 (m, 1H, H-3), 4.83 (d, 1H, *J* = 1.3 Hz, H-1), 4.23 – 4.20 (m, 1H, H-6a), 4.05 – 4.02 (m, 1H, H-6b), 3.61 – 3.59 (m, 1H, H-5), 2.12 (s, 3H, COC*H*$_3$), 2.02 (s, 3H, COC*H*$_3$), 1.95 (s, 3H, COC*H*$_3$), 1.90 (s, 3H, COC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 170.2, 170.0, 169.6, 131.9, 130.9, 128.3, 127.2, 85.6, 76.5, 71.8, 70.1, 65.8, 62.8, 20.8, 20.7, 20.6, 20.6 ppm.

Phenyl 1-thio-β-D-mannopyranoside (87)

Synthesized according to the general procedure for Zemplén deacetylation. NMR data in accordance with the literature values.[198]

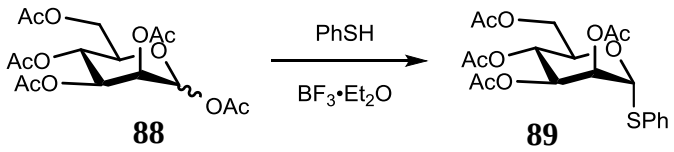


91 **87**

^{1}H NMR (400 MHz, CD_3OD): δ = 7.51 - 7.17 (m, 5H, H_{Ar}), 5.08 (d, 1H, *J* = 1.1 Hz, 1-H), 4.10 (dd, 1H, *J* = 1.1 Hz, J = 3.5 Hz, 2-H), 3.81 (dd, 1H, *J* = 2.3 Hz, *J* = 12.3 Hz, 6a-H), 3.65 – 3.62 (m, 2H, 6b-H, 3-H), 3.55 – 3.51 (m, 2H, 4-H, 5-H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 133.1, 129.9, 129.5, 128.4, 86.7 (C1), 80.4, 73.9, 72.3, 66.7, 61.2 ppm.

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (89)

Synthesized according to the general procedure for thiophenol substitution in 60% yield. NMR data in accordance with the literature values.[233]

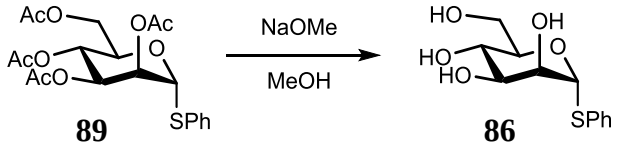


88 **89**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 - 5.27 (m, 5H, H_{Ar}), 5.57 (d, *J* = 1.6 Hz, 1H, H-1), 5.50 (dd, 1H, *J* = 1.6 Hz, *J* = 3.0 Hz, H-2), 5.31 – 5.29 (m, 2H, H-4, H-3), 4.56 – 4.54 (m, 1H, H-5), 4.28 (dd, 1H, *J* = 5.9 Hz, *J* = 12.3 Hz, H-6b), 4.08 – 4.06 (m, 1H, H-6a), 2.15 (s, 3H, COC*H*$_3$), 2.09 (s, 3H, COC*H*$_3$), 2.03 (s, 3H, COC*H*$_3$), 2.00 (s, 3H, COC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =170.4, 169.9, 169.8, 169.2, 132.5, 132.0, 129.1, 128.0, 85.9, 70.8, 69.4, 69.1, 66.3, 62.3, 20.8, 20.7, 20.7, 20.6 ppm.

Phenyl 1-thio-α-D-mannopyranoside (86)

Synthesized according to the general procedure for Zemplén deacetylation. NMR data in accordance with the literature values.[197]



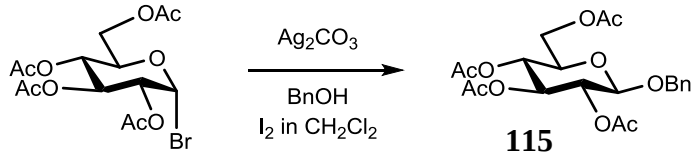
89 **86**

^{1}H NMR (400 MHz, CD_3OD): δ = 7.35–7.09 (m, 5H, H_{Ar}), 5.46 (dd, 1H, *J* = 1.6 Hz, H-1), 4.12 (dd, 1H, *J* = 1.6 Hz, *J* = 3.1 Hz, H-2), 4.06 (ddd, 1H, *J* = 2.9 Hz, *J* = 4.7 Hz, *J* = 9.1 Hz, H-5), 3.81 – 3.78 (m, 2H, H-6a, H-6b), 3.75 – 3.72 (m, 2H, H-4, H-3) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ =135.9, 132.8, 128.9, 128.2 (Ar), 90.5 (C1), 75.7 (C5), 73.1 (C2), 73.2 (C3), 68.7 (C4), 62.5 (C6) ppm.

Benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (115)[204]

A mixture of Ag_2CO_3 (32.8 mmol), benzyl alcohol (55 mmol) and a crystal of iodine in dry CH_2Cl_2 (10 mL) was stirred over 4 Å MS for 15 minutes before solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (10.9 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise. The reaction flask was covered in foil and stirred for 21 h, diluted with EtOAc, filtered through Celite and concentrated under vacuum. The residue was purified by column chromatography (Hexane:EtOAc = 5:2) to give the

our compound as a white solid in 56% yield. NMR data in accordance with the literature values.[204]

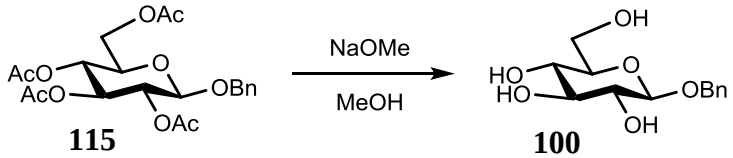


115

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5H, H_{Ar}), 5.19-5.09 (m, 2H, H-3, H-4), 4.83 (d, 1H, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.66 (d, 1H, *J* = 11.9 Hz, OC*H*$_2$Ph), 4.48 (d, 1H, *J* = 7.5 Hz, H-1), 4.23 (dd, 1H, *J* = 4.7 Hz, *J* = 12.3 Hz, H-6b), 4.10 (dd, 1H, *J* = 2.5 Hz, *J* = 12.3 Hz, H-6a), 4.05 (dd, 1H, *J* = 7.4 Hz, *J* = 9.9 Hz, H-2), 3.56 (ddd, 1H, *J* = 2.5 Hz, *J* = 4.7 Hz, *J* = 9.8 Hz, H-5), 2.07 (s, 3H, COC*H*$_3$), 2.05 (s, 3H, COC*H*$_3$), 2.03 (s, 3H, COC*H*$_3$), 2.00 (s, 3H, COC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 134.5, 127.1, 98.8, 69.9, 69.6, 67.7, 66.3, 60.2, 19.6, 19.5 ppm.

Benzyl β-D-glucopyranoside (100)

Synthesized according to the general procedure for Zemplén deacetylation. NMR data in accordance with the literature values.[235]



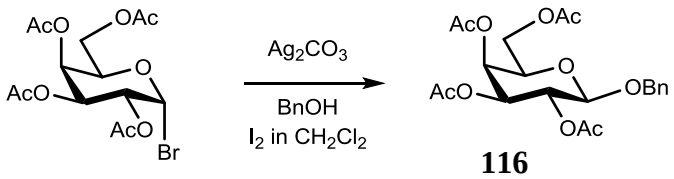
115 **100**

^{1}H NMR (400 MHz, CD_3OD): δ = 7.26–7.39 (m, 5H, H_{Ar}), 4.95 (d, 1H, *J* = 11.9 Hz, OC*H*$_2$Ph), 4.69 (d, 1H, *J* = 11.9 Hz, OC*H*$_2$Ph), 4.37 (d, 1H, *J* = 7.7 Hz, H-1), 3.91 (dd, 1H, *J* = 2.2 Hz, *J* = 12.2 Hz, H-6b), 3.72 (dd, 1H, *J* = 5.5 Hz, *J* = 11.9 Hz, H-6a) 3.31–3.34 (m, 4H, H-2, H-3, H-4, H-5) ppm. ^{13}C NMR (CD_3OD): δ =139.0, 129.2, 129.1, 128.3, 103.2 (C1), 78.0 (C5), 77.5 (C3), 75.1 (C2), 71.7 (O*C*H_2Ph), 71.6 (C4), 62.8 (C6) ppm.

Benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (116)[204]

A mixture of Ag_2CO_3 (32.8 mmol), benzyl alcohol (55 mmol) and a crystal of iodine in dry CH_2Cl_2 (10 mL) was stirred over 4 Å MS for 15 minutes before solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (10.9 mmol) in dry CH_2Cl_2 (10

mL) was added dropwise. The reaction flask was covered in foil and stirred for 21 h, diluted with EtOAc, filtered through Celite and concentrated under vacuum. The residue was purified by column chromatography (Hexane:EtOAc = 5:2) to give the our compound as a colorless syrup in 68% yield. NMR data in accordance with the literature values.[236]

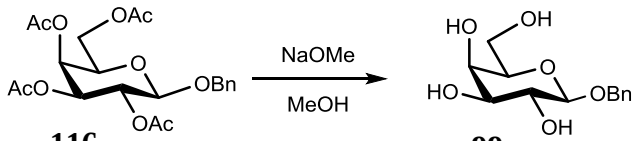


116

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.22 (m, 5H, H_{Ar}), 5.30 (d, 1H, *J* = 3.1 Hz, H-4), 5.22 (dd, 1H, *J* = 8.0 Hz, *J* = 10.5 Hz, H-2), 4.91 (dd, 1H, *J* = 3.2 Hz, *J* = 10.4 Hz, H-3), 4.84 (d, 1H, *J* = 12.1 Hz, O*CH*$_2$Ph), 4.56 (d, 1H, *J* = 12.0 Hz, O*CH*$_2$Ph), 4.44 (d, 1H, *J* = 7.9 Hz, H-1), 4.15 – 4.05 (m, 2H, H-6a, H-6b), 3.81 – 3.76 (m, 1H, H-5), 2.05 (s, 3H, COC*H*$_3$), 2.03 (s, 3H, COC*H*$_3$), 1.99 (s, 3H, COC*H*$_3$), 1.98 (s, 3H, COC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 134.5, 127.1, 98.8, 69.9, 69.6, 67.7, 66.3, 60.2, 19.6, 19.5 ppm.

Benzyl β-D-galactopyranoside (99)

Synthesized according to the general procedure for Zemplén deacetylation. NMR data in accordance with the literature values.[237]

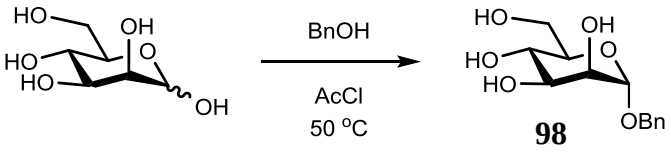


116 **99**

^{1}H NMR (400 MHz, CD_3OD): δ = 7.26–7.39 (m, 5H, H_{Ar}), 4.95 (d, 1H, *J* = 11.8 Hz, O*CH*$_2$Ph), 4.68 (d, 1H, *J* = 11.8 Hz, O*CH*$_2$Ph), 4.34 (d, 1H, *J* = 7.7 Hz, H-1), 3.88 (dd, 1H, *J* = 1.1 Hz, J = 3.4 Hz, H-4), 3.80 – 3.76 (m, 2H, H-6a, H-6b), 3.61 – 3.59 (m, 1H, H-5), 3.50 – 3.46 (m, 2H, H-2, H-3) ppm. ^{13}C NMR (CD_3OD): δ =139.0, 138.9, 129.2, 128.5, 103.8, 76.5, 74.7, 72.4, 71.3, 70.1, 62.1 ppm.

Benzyl α-D-mannopyranoside (98)[203]

A solution of D-mannose (55.5 mmol) in 80 mL of benzyl alcohol containing 4mL of acetyl chloride was heated at 50 °C for 2 h and then cooled to room temperature. Benzyl alcohol was removed with a high vacuum pump at 75 °C. The residue was then triturated with ethyl acetate to form a precipitate. The precipitate was collected by filtration and washed with ethyl acetate to give the product in 45% yield. NMR data in accordance with the literature values.[238]

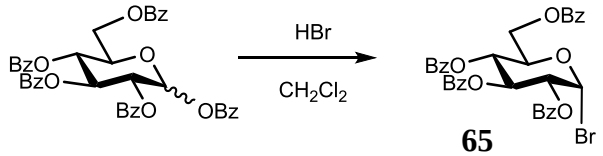


98

^{1}H NMR (400 MHz, CD_3OD): δ = 7.25-7.38 (m, 5H, H_{Ar}), 5.44 (d, 1H, *J* = 1.6 Hz, H-1), 4.07 (dd, 1H, *J* = 1.9 Hz, *J* = 3.3 Hz, H-2), 3.92 (dd, 1H, *J* = 3.4 Hz, *J* = 9.5 Hz, H-3), 3.67-3.75 (m, 3H, H-4, H-6a, H-6b), 3.60 – 3.58 (m, 1H, H-5) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 129.4, 129.1, 128.8, 128.6, 100.6 (C1), 74.9 (C5), 72.6 (C3), 72.2 (C2), 69.9 (CH_2Ph), 68.8 (C4), 62.4 (C6) ppm.

Tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (65)[229]

To the solution of penta-*O*-benzoyl-D-glucopyranose (28.5 mmol) in CH_2Cl_2 (200 mL) 33% HBr in AcOH solution (50 mL) was added. The reaction mixture was stirred at room temperature under argon for 3 hours. Then ice-cold water was added. The organic phase was washed with saturated $NaHCO_3$ solution twice and with water twice, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was crystallized from Et_2O to give the product as a white solid in 89% yield. NMR data in accordance with the literature values.[239]



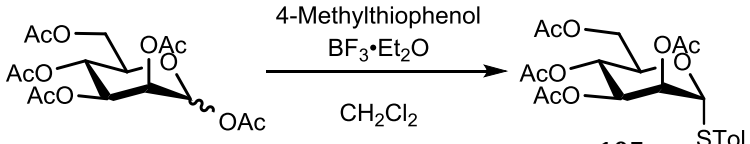
65

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 - 8.10 (m, 8H, H_{Ar}), 7.26 - 7.58 (m, 12H, H_{Ar}), 6.79 (d, 1H, *J* = 4.0 Hz, H-1), 6.19 (t, 1H, *J* = 9.8 Hz, H-3), 5.75 (t, 1H, *J* = 10.0 Hz, H-4), 5.26 (dd, 1H, *J* = 4.0 Hz, *J* = 10.0 Hz, H-2), 4.65 – 4.63 (m, 1H, H-5), 4.60

(dd, 1H, *J* = 2.7 Hz, *J* = 12.5 Hz, H-6b), 4.44 (dd, 1H, *J* = 4.5 Hz, *J* = 12.5 Hz, H-6a) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =166.1, 165.5, 165.1, 165.0, 133.8, 133.7, 133.4, 133.2, 130.0, 129.8, 129.7, 128.7, 128.4, 128.3, 128.3, 86.8 (C1), 72.7 (C5), 71.4 (C2), 70.5 (C3), 67.8 (C4), 61.9 (C6) ppm.

***p*-Methylphenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (105)**[213]

Penta-*O*-acetyl-D-mannose (41 mmol) and 4-methylthiophenol (61 mmol) were dissolved in CH_2Cl_2 (200 mL) and the mixture was cooled to 0 °C, followed by addition of $BF_3{\cdot}Et_2O$ (53 mmol). The reaction was stirred 72 h. After that time, saturated aqueous $NaHCO_3$ and solid $NaHCO_3$ were added to neutralize the mixture. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (Heptane:EtOAc= 5:2) to give the product in 60% yield. NMR data in accordance with the literature values.[213]

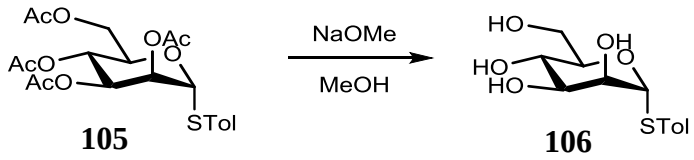


90 **105**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, 2H, *J* = 8.1 Hz), 7.12 (d, 2H, *J* = 8.1 Hz), 5.42 (dd, 1H, *J* = 1.7 Hz, *J* = 2.6 Hz, H-2), 5.34 (d, 1H, *J* = 1.6 Hz, H-1), 5.25 – 5.22 (m, 2H, H-4, H-3), 4.48 – 4.46 (m, 1H, H-5), 4.22 (dd, 1H, *J* = 5.9 Hz, *J* = 12.2 Hz, H-6a), 4.03 (dd, 1H, *J* = 2.3 Hz, *J* = 12.2 Hz, H-6b), 2.25 (s, 3H, COC*H*$_3$), 2.07 (s, 3H, COC*H*$_3$), 2.0 (s, 3H, COC*H*$_3$), 1.97 (s, 3H, COC*H*$_3$), 1.94 (s, 3H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.2, 170.1, 170.0, 138.6, 137.9, 128.5, 124.3 (C_{Ar}), 86.3, 75.9, 71.1, 69.6, 66.5, 62.6, 21.4, 21.2, 21.2, 21.1, 21.0 ppm.

***p*-Tolyl 1-thio-α-D-mannopyranoside (106)**

Synthesized according to the general procedure for Zemplén deacetylation. NMR data in accordance with the literature values.[181]



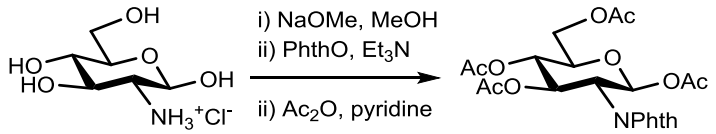
105 **106**

^{1}H NMR (400 MHz, CD_3OD): δ = 7.13–7.26 (m, 2H, H_{Ar}), 6.88–7.03 (m, 2H, H_{Ar}), 5.37 (s_{br}, 1H, H-1), 4.12 (s_{br}, 1H, H-2), 3.82-4.02 (m, 3H, H-5, H-3, H-4), 3.76 – 3.74 (m, 1H, H-6a), 3.65 (d, 1H, *J* = 12.0 Hz, H-6b), 3.41 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 138.7, 133.4, 130.7, 130.6, 90.7 (C1), 76.1 (C5), 74.3 (C2), 73.4 (C4), 68.5 (C3), 62.5 (C6), 21.0 (CH_3-Tol) ppm.

1,3,4,6-Tetra-*O*-acetyl-2-phthalimido-2-deoxy-β-D-glucopyranose (94)[240]

A 1 M NaOMe solution was prepared by adding metallic sodium (0.232 mol) in small pieces to MeOH (230 mL) at –5 °C in a 500 mL round-bottomed flask equipped with a reflux condenser, which was swirled until the metal had been completely consumed. This was slowly added at 0 °C to a 1 L round-bottomed flask containing glucosamine hydrochloride (0.232 mol). The reaction mixture was vigorously stirred for 2 hours at rt and then treated with finely ground phthalic anhydride (0.128 mol) and stirred for another 45 min. The mixture was charged with a second portion of phthalic anhydride (0.128 mol), Et_3N (0.255 mol), and MeOH (230 mL) and vigorously stirred for another 24 h, during which it slowly changed from a milky white solution to a thick yellow paste. The intermediate phthalamate were precipitated as a white solid by cooling the mixture to – 20 °C for 4 h. This was filtered off and thoroughly washed with cold MeOH, then dried overnight under reduced pressure. The solid was redispersed in pyridine (500 mL) with vigorously stirring and cooled to –5 °C, followed by treatment with Ac_2O (330 mL). The mixture was stirred at r.t. for 48 h, during which it slowly changed from a translucent white to an opaque yellow solution. Cold EtOH (100 mL) was slowly added to the mixture to quench the excess Ac_2O, and the solution was then concentrated by rotary evaporation. The residue was redispersed in toluene (3x100 mL) and concentrated several times for the azeotropic removal of pyridine. The remaining slurry was redissolved in CH_2Cl_2 (500 mL) and washed with H_2O (4 x 250 mL) and brine (250 mL), then dried (Na_2SO_4) and evaporated to dryness. The crude product was dissolved in minimal amount of hot EtOAc (100 mL), then diluted with hexanes (400 mL) and left to cool at –5 °C. The crystallized product was collected by filtration,

washed with cold hexanes, and dried to obtain the desired tetraacetate in 72% yield. NMR data in accordance with the literature values.[240]

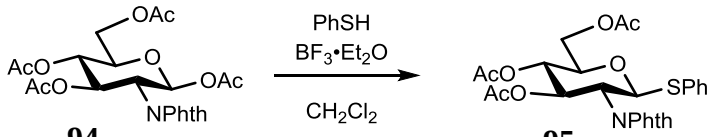


93 **94**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 - 7.74 (m, 2H, H_{Ar}), 7.73-7.63 (m, 2H, H_{Ar}), 6.45 (d, 1H, *J* = 8.9 Hz, H-1), 5.90 (dd, 1H, *J* = 9.2 Hz, *J* = 10.6 Hz, H-3), 5.22 (t, 1H, *J* = 9.2 Hz, H-4,), 4.48 (dd, 1H, *J* = 8.9 Hz, *J* = 10.6 Hz, H-2), 4.38 (dd, 1H, *J* = 4.3 Hz, *J* = 12.4 Hz, H-6a), 4.20 – 4.19 (m, 1H, H-6b), 4.02 – 4.00 (m, 1H, H-5), 2.13 (s, 3H, COC*H*$_3$), 2.05 (s, 3H, COC*H*$_3$), 2.01 (s, 3H, COC*H*$_3$), 1.88 (s, 3H, COC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.0, 169.5, 168.6, 167.4 (2x CO), 134.5, 123.8, 89.8, 72.6, 70.5, 68.3, 61.5, 53.5, 20.8, 20.7, 20.6, 20.4 ppm.

Phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (95)

Synthesized according to the general procedure for thiophenol substitution in 70% yield. Instead of $BF_3{\cdot}Et_2O$, TMSOTf was used.[240] NMR data in accordance with the literature values.[233]

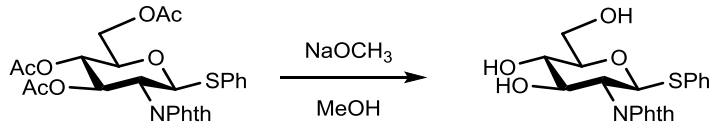


94 **95**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 - 7.69 (m, 4H, NPhth), 7.48 - 7.25 (m, 5H, SPh), 5.72 (t, 1H, *J* = 9.5 Hz, H-3), 5.64 (d, 1H, *J* = 10.5 Hz, H-1), 5.07 (t, 1H, *J* = 9.6 Hz, H-4), 4.29 (t, 1H, *J* = 10.4 Hz, H-2), 4.22 – 4.20 (m, 1H, H-6a), 4.14 – 4.12 (m, 1H, H-6b), 3.91 – 3.90 (m, 1H, H-5), 2.03 (s, 3H, COC*H*$_3$), 1.96 (s, 3H, COC*H*$_3$), 1.77 (s, 3H, COC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 170.0, 169.3, 167.7, 166.8, 134.2, 134.3, 133.2, 131.4, 131.1, 131.0, 128.8, 128.3, 123.6, 83.4, 75.8, 71.5, 68.7, 62.1, 53.4, 20.6, 20.6, 20.5 ppm.

Phenyl 2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (92)

Synthesized according to the general procedure for Zemplén deacetylation. NMR data in accordance with the literature values.[241]

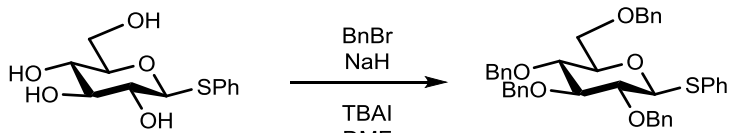


95 **92**

^{1}H NMR (400 MHz, CD_3OD): δ = 7.90 - 7.75 (m, 4H, NPhth), 7.42 - 7.26 (m, 5H, SPh), 5.46 (d, 1H, *J* = 10.3 Hz, H-1), 4.20 (dd, 1H, *J* = 8.2 Hz, *J* = 10.4 Hz, H-2), 4.05 (t, 1H, *J* = 10.2 Hz, H-3), 3.92 -3.90 (m, 1H, H-4), 3.66 (dd, 1H, *J* = 5.2 Hz, *J* = 12.0 Hz, H-6a), 3.45-3.33 (m, 2H, H-5, H-6b) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 167.5 (2xCO), 133.8, 132.9, 124.5, 123.4, 86.5, 86.2, 72.3, 69.6, 63.4, 61.2 ppm.

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (66)

Synthesized according to the general procedure for benzylation. After completion (5 hours), the reaction mixture was quenched with glacial acetic acid until pH was neutral. Then 50 mL of water was added and the mixture was cooled to 0 °C. White crystals were filtered off and recrystallized from EtOH and dried at high vacuum to give the pure product in 76% yield. NMR data in accordance with the literature values.[182]

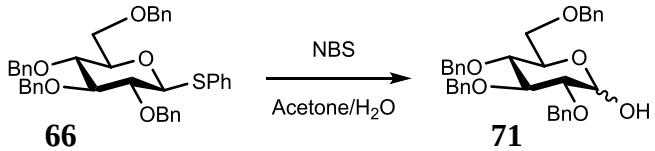


61 **66**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 - 7.46 (m, 2H, H_{Ar}), 7.36 - 7.05 (m, 23H, H_{Ar}), 4.81 - 4.91 (m, 3H, OC*H*$_2$Ph), 4.72 (d, 1H, *J* = 10.3 Hz, OC*H*$_2$Ph), 4.67 (d, 1H, *J* = 9.7 Hz, H-1), 4.55-4.42 (m, 4H, OC*H*$_2$Ph), 3.75-3.53 (m, 4H, H-3, H-4, H-6), 3.50-3.40 – 3.37 (m, 2H, H-2, H-5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 138.1, 137.8, 133.7, 131.7, 128.7-127.2 (C_{Ar}), 87.1 (C1), 86.5 (C3), 80.5 (C2), 78.9 (C5), 77.3 (C4), 75.2 (O*C*H$_2$Ph), 75.2 (O*C*H$_2$Ph), 74.6 (O*C*H$_2$Ph), 73.1 (O*C*H$_2$Ph), 68.7 (C6) ppm.

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (71)

Synthesized according to the general procedure for thiophenol cleavage in 88% yield. NMR data in accordance with the literature values.[242]

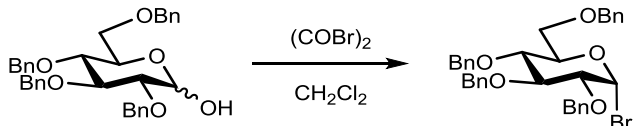


66 **71**

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33 - 7.13 (m, 20H, H_{Ar}), 5.19 (d, 1H, *J* = 2.2 Hz, H-1), 4.87-4.43 (m, 8H, OC*H*$_2$Ph), 4.10 - 4.02 (m, 1H, H-5), 4.00 (t, 1H, *J* = 9.8 Hz, H-3), 3.65-3.42 (m, 4H, H-2, H-4, H-6ab) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 138.1, 137.8, 128.5, 128.4, 128.1, 128.1, 128.0, 127.8, 127.7, 127.6, 127.6, 91.2, 81.7, 80.0, 77.8, 75.7, 75.0, 73.4, 73.1, 70.1, 68.6 ppm.

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl bromide (70)

Synthesized according to the general procedure for bromination. Product was obtained as a colorless syrup in 85% yield. NMR data in accordance with the literature values.[185]

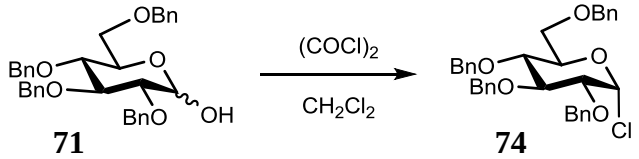


71 **70**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 - 7.14 (m, 20H, H_{Ar}), 6.35 (d, 1H, *J* = 3.7 Hz, H-1), 4.89 (d, 1H, *J* = 10.8 Hz, OC*H*$_2$Ph), 3.79 - 3.69 (m, 2H, OC*H*$_2$Ph), 4.63 (s, 2H, OC*H*$_2$Ph), 4.49 (d, 1H, *J* = 12.1 Hz, OC*H*$_2$Ph), 4.43 (d, 1H, *J* = 10.8 Hz, OC*H*$_2$Ph), 4.38 (d, 1H, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.00-3.92 (m, 1H, H-5), 3.74-3.62 (m, 3H, H-3, H-4, H-6a), 3.57 (dd, 1H, *J* = 2.0 Hz, *J* = 11.0 Hz, H-6b), 3.45 (dd, 1H, *J* = 3.8 Hz, *J* = 9.3 Hz, H-2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2-137.2 (C_{Ar}), 128.4-127.2 (CH_{Ar}), 91.7 (C1), 82.0 (C3), 79.4 (C2), 76.6 (OCH_2Ph), 75.7 (OCH_2Ph), 75.1 (OCH_2Ph), 73.4 (OCH_2Ph), 72.7 (C5), 67.4 (C6) ppm.

2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl chloride (74)

Synthesized according to the general procedure for chlorination in 75% yield. NMR data in accordance with the literature values.[146]

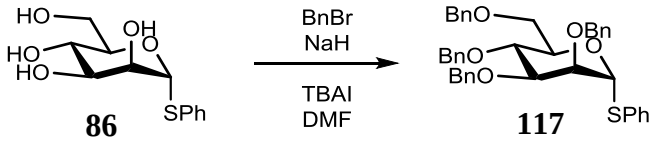


71 **74**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 - 7.13 (m, 20H, H_{Ar}), 6.10 (d, 1H, *J* = 3.5 Hz, H-1), 4.86 - 4.45 (m, 8H, OCH_2Ph), 4.21 - 4.12 (m, 2H), 3.80 (dd, 1H, *J* = 2.5, *J* = 11.2 Hz, H-6a), 3.76 – 3.73 (m, 2H), 3.61 (dd, 1H, *J* = 2.2, *J* = 11.0 Hz, H-6b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 138.1, 137.8, 137.6, 129.3-127.2, 91.3, 81.8, 80.0, 76.8, 75.0, 73.5, 73.2, 70.3, 68.6 ppm.

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside (117)

Synthesized according to the general procedure for benzylation. After completion, reaction mixture was quenched with glacial acetic acid until pH was neutral and then transferred to extraction with 200 mL of CH_2Cl_2. Next, organic phase was washed with water (4x100 mL), dried with $MgSO_4$ and evaporated to give brownish syrup. The syrup was subjected to column chromatography (heptan/EtOAc= 3:1) and a yellowish syrup was collected as the product in a 65% yield. NMR data in accordance with the literature values.[243]



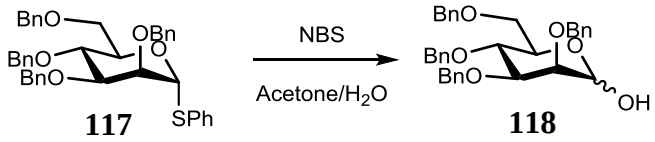
86 **117**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 - 7.22 (m, 25H, H_{Ar}), 5.58 (d, 1H, *J* = 1.5 Hz, H-1), 4.86 (d, 1H, *J* = 10.6 Hz, OCH_2Ph), 4.70 (d, 1H, *J* = 12.2 Hz, OCH_2Ph), 4.68 - 4.65 (m, 4H, 2xOCH_2Ph), 4.50 (d, 1H, *J* = 10.7 Hz, OCH_2Ph), 4.43 (d, 1H, *J* = 12.0 Hz, OCH_2Ph), 4.32 - 4.25 (m, 1H, H-5), 4.07 (t, 1H, *J* = 9.2 Hz, H-4), 3.97 - 3.95 (m, 1H, H-2), 3.86 - 3.81 (m, 2H, H-3, H-6b), 3.73 (dd, 1H, *J* = 1.8 Hz, *J* = 11.2 Hz, H-6a) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 138.2, 138.2, 138.0, 135.7,

130.0-127.1 (CH_{Ar}), 87.5 (C1), 84.1 (C3), 79.9 (C5), 77.3 (C2), 75.1 (OCH_2Ph), 75.0 (OCH_2Ph), 74.8 (C4), 73.3 (OCH_2Ph), 72.3 (OCH_2Ph), 69.7 (C6) ppm.

2,3,4,6-Tetra-*O*-benzyl-D-mannopyranose (118)

Synthesized according to the general procedure for thiophenol cleavage in 61% yield. NMR data in accordance with the literature values.[242]

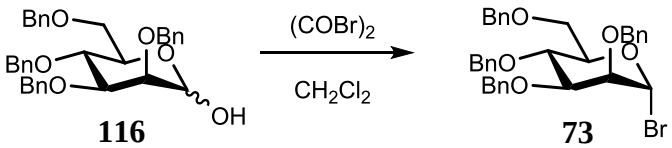


117 **118**

^{1}H NMR (400 MHz, $CDCl_3$,): δ = 7.28 - 7.05 (m, 20H, H_{Ar}), 5.20 (s, 1H, H-1), 4.90 – 4.75 (m, 8H, OCH_2Ph), 4.09 - 4.05 (m, 1H, H-5), 3.95 (dd, 1H, *J* = 3.2 Hz, *J* = 9.2 Hz, H-2), 3.83 (t, 1H, *J* = 9.5 Hz, H-3), 3.81-3.74 (m, 2H, H-4, H-6a), 3.40 (s, 1H, H-6b) ppm. (100 MHz, $CDCl_3$): δ = 138.5, 138.4, 138.4, 138.3, 128.6, 128.5, 128.3, 128.0, 127.9, 127.3, 127.1, 126.6, 92.6, 79.7, 75.1, 74.9, 74.8, 73.2, 72.6, 72.2, 71.5, 69.4 ppm.

2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosyl bromide (73)

Synthesized according to the general procedure for bromination. Product was obtained as a brownish syrup in 46% yield. NMR data in accordance with the literature values.[146]



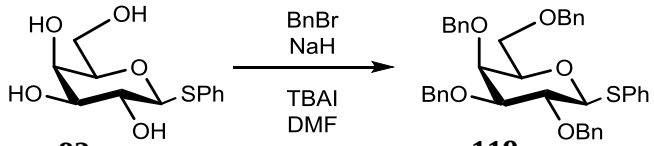
116 **73**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 - 7.10 (m, 20H, H_{Ar}), 6.42 (d, 1H, *J* = 1.0 Hz, H-1), 4.91 (d, 1H, *J* = 10.9 Hz, O*CH*$_2$Ph), 4.69 - 4.58 (m, 4H, O*CH*$_2$Ph), 4.57 (d, 1H, *J* = 11.7 Hz, O*CH*$_2$Ph), 4.53 (d, 1H, *J* = 10.8 Hz, O*CH*$_2$Ph), 4.47 (d, 1H, *J* = 12.1 Hz, O*CH*$_2$Ph), 4.28 (dd, 1H, *J* = 3.2 Hz, *J* = 9.3 Hz, H-3), 4.10 (dd, 1H, *J* = 9.4 Hz, *J* = 9.7 Hz, H-4), 3.97 - 3.91 (m, 2H, 2-H, H-5), 3.82 (dd, 1H, *J* = 4.1 Hz, *J* = 11.2 Hz, H-6a), 3.68 (dd, 1H, *J* = 1.8 Hz, *J* = 11.2 Hz, H-6b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 138.0, 137.6 (C_{Ar}), 128.9, 128.8, 128.5, 128.4, 128.3, 128.1, 128.0,

127.9, 127.8, 127.7, 127.6, 127.5 (CH_{Ar}), 88.2 (C1), 78.6 (C5), 78.4 (C3), 76.1 (C2), 75.3 (OCH_2Ph), 74.0 (C4), 73.4 (OCH_2Ph), 72.9 (OCH_2Ph), 72.5 (OCH_2Ph), 69.0 (C6) ppm.

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-galactopyranoside (119)

Synthesized according to the general procedure for benzylation. After completion, the reaction mixture was quenched with glacial acetic acid until pH was neutral. Then 50 mL of water was added and the mixture was cooled to 0 °C. White crystals were filtered off and recrystallized from EtOH and dried at high vacuum to give the pure product in 76% yield. NMR data in accordance with the literature values.[182]

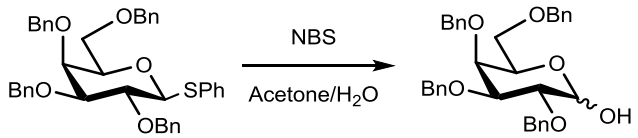


82 **119**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 - 7.22 (m, 25H, H_{Ar}), 4.92 (d, 1H, *J* = 11.1 Hz, OC*H*$_2$Ph), 4.76 (d, 1H, *J* = 10.5 Hz, OC*H*$_2$Ph), 4.72-4.66 (m, 3H, OC*H*$_2$Ph), 4.63 (d, 1H, *J* = 9.6 Hz, H-1), 4.59 (d, 1H, *J* = 11.1 Hz, OC*H*$_2$Ph), 4.47 (d, 1H, *J* = 11.2 Hz, OC*H*$_2$Ph), 4.40 (d, 1H, *J* = 11.4 Hz, OC*H*$_2$Ph), 3.96 (d, 1H, *J* = 2.6 Hz, H-4), 3.90 (t, 1H, *J* = 9.1 Hz, H-2), 3.62- 3.55 (m, 4H, H-3, H-5, H-6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 138.2, 138.1, 137.8, 135.5, 131.3-126.3 (CH_{Ar}), 87.7 (C1), 84.1 (C3), 77.2 (C2) 76.9 (C5), 75.6 (OCH_2Ph), 74.4 (OCH_2Ph), 73.5 (OCH_2Ph), 73.5 (C4), 72.7 (OCH_2Ph), 68.7 (C6) ppm.

2,3,4,6-Tetra-*O*-benzyl-D-galactopyranose (120)

Synthesized according to the general procedure for thiophenol cleavage in 55% yield. NMR data in accordance with the literature values.[242]



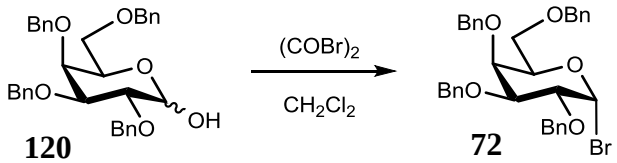
119 **120**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 - 7.12 (m, 20H, H_{Ar}), 5.28 (s, 1H, H-1), 4.90 - 4.72 (m, 8H, OCH_2Ph), 4.14 - 4.08 (m, 1H, H-5), 4.03(dd, 1H, *J* = 3.6 Hz, *J* = 10.9

Hz, H-2), 3.90 - 3.85 (m, 1H, H-3), 3.55 - 3.35 (m, 3H, H-4, H-6a, H-6b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 138.5, 138.2, 137.8 (C_{Ar}), 128.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.8, 127.7, 127.6, (CH_{Ar}), 97.8 (C1), 82.2 (C3), 80.7 (C2), 75.1, 74.5, 74.4, 72.9 (OCH_2Ph), 73.6 (C-4), 73.6 (C-5), 68.9 (C-6) ppm.

2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl bromide (72)

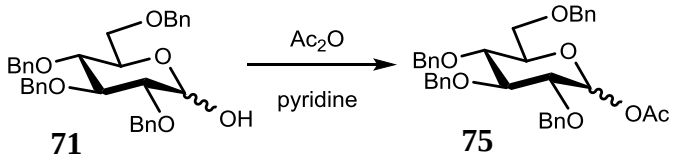
Synthesized according to the general procedure for bromination. Product was obtained as a colorless syrup in 87% yield. NMR data in accordance with the literature values.[146]



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 - 7.18 (m, 20H, H_{Ar}), 6.45 (d, 1H, *J* = 3.8 Hz, H-1), 4.92 (d, 1H, *J* = 11.5 Hz, OC*H*$_2$Ph), 4.83 (d, 1H, *J* = 11.6 Hz, OC*H*$_2$Ph), 4.74 (d, 1H, *J* = 11.9 Hz, OC*H*$_2$Ph), 4.69 (d, 1H, *J* = 11.7 Hz, OC*H*$_2$Ph), 4.62 (d, 1H, *J* = 11.9 Hz, OC*H*$_2$Ph), 4.54 (d, 1H, *J* = 11.5 Hz, OC*H*$_2$Ph), 4.48 (d, 1H, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.40 (d, 1H, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.25 - 4.19 (m, 1H, H-5), 4.17 (dd, 1H, *J* = 3.7 Hz, *J* = 9.8 Hz, H-2), 3.98 – 3.96 (m, 1H, H-4), 3.96 (dd, 1H, *J* = 2.6 Hz, *J* = 9.6 Hz, H-3), 3.55 (dd, 1H, *J* = 6.8 Hz, *J* = 9.5 Hz, H-6a), 3.51 (dd, 1H, *J* = 6.2 Hz, *J* = 9.4 Hz, H-6b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ =138.4, 138.3, 137.7, 137.6 (C_{Ar}), 128.3, 128.3, 128.2, 128.2, 127.8, 127.8, 127.7, 127.6, 127.5, 127.4 (CH_{Ar}), 94.7 (C1), 78.2 (C3), 76.0 (C2), 75.0 (OCH_2Ph), 74.3 (C4), 73.4 (OCH_2Ph), 73.3 (OCH_2Ph), 73.0 (OCH_2Ph), 72.3 (C5), 68.0 (C6) ppm.

1-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (75)[244]

A mixture of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranose (3.7 mmol), pyridine (48 mmol), and Ac_2O (112 mmol) was stirred at room temperature for 24 h. The reaction was quenched with crushed ice, transferred to extraction funnel with CH_2Cl_2 (200 mL) and washed with cold H_2O (3 × 200 mL). The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated under vacuum to yield the product as a colorless oil in the 55% yield. NMR data in accordance with the literature values.[245]

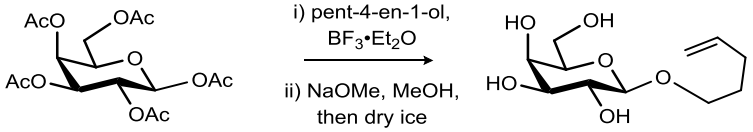


71 **75**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 - 7.12 (m, 40H, H_{Ar}), 6.30 (d, 1H, H-1α), 5.60 (d, 1H, H-1β), 4.50 - 4.91 (m, 16H, OCH_2Ph), 3.92 – 3.88 (m, 4Hα, H-2, H-3, H-4, H-5), 3.82 – 3.76 (m, 4Hβ, H-2, H-3, H-4, H-5), 3.54 – 3.51 (m, 2Hβ, H-6), 3.45 – 3.41 (m, 2Hα, H-6) 2.04 (s, 3H, OC*H*$_3$), 1.95 (s, 3H, OC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 169.4 (2xC=O), 138.6-137.5 (8C, C_{Ar}), 94.3, 90.8, 82.4, 78.6, 78.1, 77.4, 75.4, 75.3, 74.9, 74.7, 74.5, 74.1, 73.6, 73.5, 73.4, 72.9, 71.8, 68.4, 67.9, 21.2, 21.0 ppm.

Pent-4-enyl β-D-galactopyranoside (96)[202]

To a solution of galactose pentaacetate (89.7 mmol) and pent-4-en-1-ol (194 mmol) in CH_2Cl_2 (250 mL) was added $BF_3{\cdot}OEt_2$ (110 mmol). The mixture was stirred at rt under an atmosphere of nitrogen for 10 h, and then diluted with CH_2Cl_2 (100 ml) and washed with saturated aq. $NaHCO_3$ (350 ml). The organic layer was dried and concentrated. The syrupy residue was dissolved in 0.04 M NaOMe in MeOH (300 ml) and the solution stirred for 2 h. The mixture was quenched with dry ice, concentrated and purified by flash chromatography (CH_2Cl_2–MeOH; 6:1) to give the product in 65% yield. NMR data in accordance with the literature values.[202]

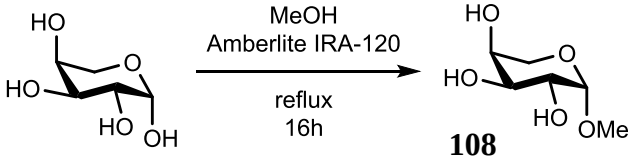


97 **96**

^{1}H NMR (400 MHz, CD_3OD): δ = 5.73 (m, 1H), 5.05 (d, 1H, *J* = 17.4 Hz), 4.96 (d, 1H, *J* = 10.2 Hz), 4.24 – 4.22 (m, 1H), 3.84 – 3.81 (m, 2H), 3.72 - 3.51 (m, 5H), 3.34 (t, 1H, *J* = 9.0 Hz), 2.17 – 2.14 (m, 2H), 1.72 – 1.70 (m, 2H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 139.0, 115.0, 103.0, 75.2, 73.0, 69.9, 69.8, 68.7, 61.0, 29.3, 28.1 ppm.

Methyl β-L-arabinopyranoside (108)[246]

A mixture of L-arabinose (73.3 mmol) and ion-exchange resin (Amberlite® IRA-120, 20.0 g) in anhydrous methanol (150 ml) was heated at reflux overnight. The cooled mixture was filtered and evaporated to a pale brown solid. This was recrystallized from ethanol to give the pure β anomer as colorless crystals in 45% yield. NMR data in accordance with literature values.[246]

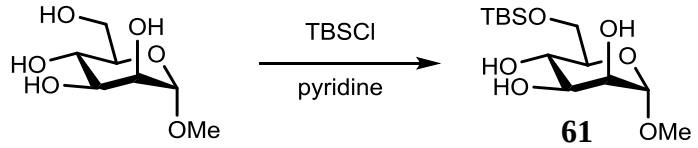


108

^{1}H NMR (400 MHz, DMSO): δ = 4.45 - 4.33 (m, 3H, 3xOH), 4.29 (d, 1H, *J* = 3.5 Hz, H-1), 3.62 – 3.61 (m, 1H, H-4), 3.58-3.51 (m, 3H, H-2, H-3, H-5), 3.42 (dd, 1H, *J* = 2.9 Hz, *J* = 11.9 Hz, H-5), 3.29 (s, 3H, OCH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 100.1, 69.0, 68.5, 68.2, 62.5, 54.4 ppm.

Methyl 6-*O*-(*tert*-butyldimethylsilyl)-α-D-mannopyranoside (61)[215]

Methyl α-D-mannopyranoside (10 mmol) and *tert*-butyldimethylsilyl chloride (12 mmol) were dissolved in pyridine (50 mL) and stirred at room temperature overnight under nitrogen. The resulting mixture was diluted with dichloromethane, washed with water, and extracted several times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was purified by silica gel chromatography (ethyl acetate:pentane=7:3) to give the pure product in 86% yield. NMR data in accordance with literature values.[215]



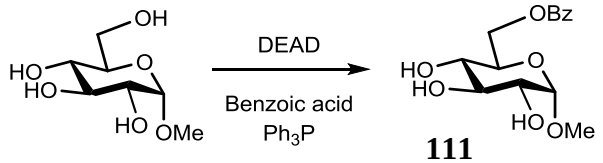
61

^{1}H NMR (400 MHz, CD_3OD): δ = 4.61 (d, 1H, *J* = 1.3 Hz, H-1), 3.98 (dd, 1H, *J* = 1.6 Hz, *J* = 11.2 Hz, H-6a), 3.79 - 3.75 (m, 2H, H-2, H-6b), 3.64 (dd, 1H, *J* = 3.5 Hz, *J* = 8.2 Hz, H-3), 3.56 - 3.46 (m, 2H, H-4, H-5), 3.36 (s, 3H, OCH_3), 0.92 (s, 9H, $Si(C(\mathit{CH_3})_3)(CH_3)_2$), 0.10 (s, 3H, $Si(C(CH_3)_3)(\mathit{CH_3})_2$), 0.10 (s, 3H,

$Si(C(CH_3)_3)(CH_3)_2$) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 102.6, 75.0, 72.7, 72.0, 68.8, 64.6, 55.0, 26.4, 19.2, -5.1, -5.1.

Methyl 6-*O*-benzoyl-α-D-glucopyranoside (111)[222]

A solution of benzoic acid (1 mmol) and DEAD (1.5 mmol) in 1 mL of THF was slowly added at room temperature to a stirred mixture of methyl 6-*O*-benzoyl-α-D-glucopyranoside (1 mmol) and PPh_3 (1.5 mmol) in 3 mL of THF under argon. The mixture was then stirred for 24 hours. The solvent was removed and the residue was isolated by column chromatography in diethyl ether followed by 5:1 ethyl acetate-methanol to obtain the product in a 43% yield. NMR data in accordance with literature values.[247, 220]

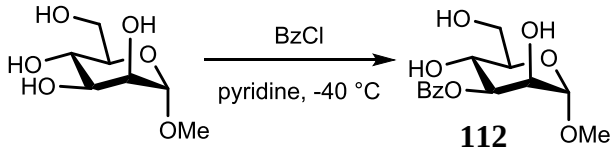


111

^1H NMR (400 MHz, CD_3OD): δ = 7.95 - 7.52 (m, 5H, H_{Ar}), 5.25 (s_{br}, 3H, 2-OH, 3-OH, 4-OH), 4.71 (dd, 1H, *J* = 3.2 Hz, *J* = 9.4 Hz, H-6), 4.58 (d, 1H, *J* = 2.1 Hz, H-1), 4.35 (dd, 1H, *J* = 6.0 Hz, *J* = 9.4 Hz, H-6), 3.69 – 3.67 (m, 1H, H-5), 3.45 – 3.44 (m, 1H, H-2), 3.32 (s, 3H, OCH_3), 3.25 – 3.20 (m, 2H, H-3, H-4) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 168.9 (C=O), 134.1, 131.9, 130.6, 129.7 (C_{Ar}), 101.0 (C-1), 74.8 (C-3), 73.6 (C-5), 73.3 (C-2), 71.6 (C-4), 62.4 (C-6), 55.5 (OCH_3) ppm.

Methyl 3-*O*-benzoyl-α-D-mannopyranoside (112)

A magnetically stirred solution of methyl α-D-mannopyranoside (1 equiv.) in anhydrous pyridine (20 mL) was cooled to -40 °C. Benzoyl chloride (1 equiv.) was added dropwise. The bath temperature was kept around -40 °C for 30 minutes and then the reaction was concentrated *in vacuo*. The residue was dissolved in dichloromethane and then washed with aqueous HCl and aqueous $NaHCO_3$ and water, and then dried with $MgSO_4$. Removal of the desiccant and the solvent gave the crude product in 70% yield. NMR data in accordance with literature values.[224]

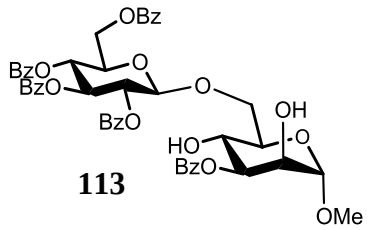


112

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, 2H, *J* = 7.3 Hz), 7.51 (t, 1H, *J* = 8.2 Hz), 7.26 (t, 2H, *J* = 8.2 Hz), 5.27 (d, 1H, *J* = 9.7 Hz), 4.63 (s, 1H), 4.27 - 4.21 (m, 1H), 4.11-4.00 (m, 2H), 3.88 (s_{br}, 1H), 3.78 - 3.63 (m, 3H), 3.66 (d, 1H, *J* = 9.6 Hz), 3.27 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6 (C=O), 133.7, 132.5, 129.3, 128.1, 99.8 (C-1), 74.3 (C-3), 71.4, 68.6, 63.8, 60.5, 54.1 (OCH_3) ppm.

Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-3-*O*-benzoyl-α-D-mannopyranoside (113)

Methyl 3-*O*-benzoyl-α-D-mannopyranoside (1.0 equiv.) was stirred with diphenylborinic acid 2-aminoethyl ester (0.1 equiv.) in CH_2Cl_2 (2 mL) at room temperature under an inert gas followed by the addition of bromide donor (1.3 equiv.), NIS (2.0 equiv.) and catalytic amount of CSA (0.2 equiv.). The reaction mixture was stirred, until complete consumption of the starting material was observed by TLC. The mixture was concentrated onto silica or diluted with CH_2Cl_2, washed with saturated aqueous sodium thiosulfate and water, dried and the solvent removed in vacuo. Finally, the product was purified by flash column chromatography (Toluene:Acetone=3:1).



113

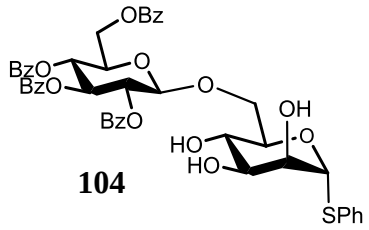
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02–7.70 (m, 25H, H_{Ar}), 5.85 (t, 1H, *J* = 9.6 Hz), 5.65 (t, 1H, *J* = 9.6 Hz), 5.48 (dd, 1H, *J* = 7.7 Hz, *J* = 9.7 Hz), 5.14 (dd, 1H, *J* = 3.2 Hz, *J* = 9.8 Hz), 4.90 (d, 1H, *J* = 7.8 Hz, H-1'), 4.64 (dd, 1H, *J* = 3.1 Hz, *J* = 12.2 Hz), 4.57 (d, 1H, *J* = 1.7 Hz, H-1), 4.40 (dd, 1H, *J* = 4.7 Hz, *J* = 12.2 Hz), 4.17 (dd, 1H, *J* = 2.2 Hz, *J* = 11.0 Hz), 4.13-4.04 (m, 1H), 3.97 (s_{br}, 1H), 3.93–3.79 (m, 2H), 3.70 (s_{br}, 1H), 3.11 (s, 3H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9,

165.3, 164.8, 164.3, 164.2, (5xC=O), 132–127 (C_{Ar}), 100.8 (C-1'), 99.6 (C-1), 74.3, 71.7, 71.3, 71.1, 70.6, 68.6, 68.4, 68.1, 67.4, 64.9, 61.7, 53.9 (O*C*H$_3$) ppm.

General Procedure for Koenigs–Knorr Glycosylation:[65] Equimolar amounts of phenyl thioglycopyranoside and phenylboronic acid were dissolved in dry DME (5 mL) to give a 50 mg/mL glycoboronate solution. MS (3 Å, 350 mg) were added, and the mixture was stirred overnight or until dry, as monitored by NMR spectroscopy. A decanted aliquot (1 mL) of this solution was added to a mixture of the bromide donor (1.3 equiv.) and MS (3 Å, 175 mg) under argon, and the resulting suspension was stirred overnight. AgOTf (1.3 equiv.) was added at 0 °C, and the reaction mixture was stirred for 3 h (TLC: toluene/acetone, 3:1). CH_2Cl_2, MeOH, and Amberlite IRA 743 (250–300 mg) were then added, and the mixture was stirred overnight. The suspension was filtered through Celite, and the pad was flushed with CH_2Cl_2/MeOH (1:1 mixture). The filtrate was concentrated and the residue was purified by flash chromatography (toluene/acetone, 7:1).

Phenyl 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→6)-1-thio-α-D-mannopyranoside (104)

Synthesized according to the general procedure for Koenigs-Knorr glycosylation. Product was obtained as a solid in 15% yield. NMR data in accordance with the literature values.[172]

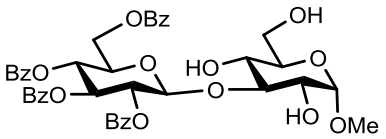


104

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–7.05 (m, 25H, H_{Ar}), 5.82 (t, 1H, *J* = 9.5 Hz, H-3'), 5.61 (t, 1H, *J* = 9.7 Hz, H-4'), 5.49-5.40 (m, 2H, H-2', H-1), 4.85 (d, 1H, *J* = 7.8 Hz, H-1'), 4.59 (dd, 1H, *J* = 3.7, *J* = 12.2 Hz, H-6'a), 4.36 (dd, 1H, *J* = 4.9, *J* = 12.2 Hz, H-6'b), 4.16 - 3.98 (m, 4H), 3.88 (dd, 1H, *J* = 4.0, *J* = 11.1 Hz, H-6b), 3.68–3.57 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 164.8, 164.5, 164.1 (4xC=O), 133–127 (C_{Ar}), 100.7 (C-1'), 86.9 (C-1), 71.7 (C-3'), 71.4 (C-2'), 71.1, 70.8 (3xC), 68.5 (C-5'), 68.1 (C-6), 67.4 (C-5), 61.9 (C-6') ppm.

Methyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl-(1→3)-α-D-glucopyranoside (107)

Synthesized according to the general procedure for Koenigs-Knorr glycosylation. Product was obtained as a colorless syrup in 15% yield. NMR data in accordance with the literature values.[178]



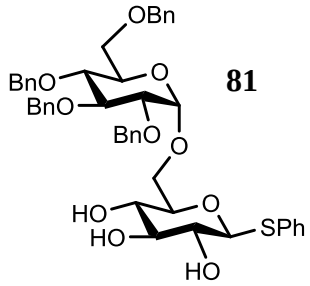
107

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 - 7.25 (m, 20H, H_{Ar}), 5.92 (t, 1H, *J* = 9.8 Hz, H-3ˈ), 5.61 (t, 1H, *J* = 9.8 Hz, H-4ˈ), 5.55 (dd, 1H, *J* = 8.1 Hz, *J* = 9.8 Hz, H-2ˈ), 5.03 (d, 1H, *J* = 8.0 Hz, H-1ˈ), 4.77 (dd, 1H, *J* = 2.7 Hz, *J* = 12.3 Hz, H-6ˈb), 4.65 (d, 1H, *J* = 3.9 Hz, H-1), 4.37 (dd, 1H, *J* = 6.8 Hz, *J* = 12.3 Hz, H-6ˈa), 4.24 – 3.23 (m, 1H, H-5ˈ), 3.83 (dd, 1H, *J* = 3.3 Hz, *J* = 11.7 Hz, H-6b), 3.75 (dd, 1H, *J* = 4.3 Hz, *J* = 11.7 Hz, H-6a), 3.72 (t, 1H, *J* = 9.0 Hz, H-3), 3.58 (ddd, 1H, *J* = 3.3 Hz, *J* = 4.3 Hz, *J* = 9.2 Hz, H-5), 3.54 (t, 1H, *J* = 9.0 Hz, H-4), 3.51 (dd, 1H, *J* = 3.9 Hz, *J* = 9.0 Hz, H-2), 3.36 (s, 3H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 165.5, 165.5, 165.1, 133.6 - 127.2, 102.5 (C1ˈ), 98.9 (C1), 87.1 (C3), 72.5 (C3ˈ), 72.7 (C5ˈ), 72.1 (C2ˈ), 71.0 (C5), 70.7 (C4), 69.5 (C2), 69.3 (C4ˈ), 62.9 (C6ˈ), 62.7 (C6), 55.1 (OCH_3) ppm.

General Procedure for Tin-Mediated Glycosylation with Perbenzylated Glycosyl Bromide: A suspension of the unprotected hexopyranoside (0.5 mmol) and Bu_2SnO (0.75 mmol) in MeOH (3.0 mL) was refluxed until a clear solution was obtained (3 h). The solvent was evaporated in vacuo followed by drying at high vacuum for 6 h to give the stannylene derivative as a colorless foam. The bromide donor (0.9 mmol) and 4 Å MS (300 mg) were added to a solution of the stannylene derivative in CH_2Cl_2 (2 mL). The suspension was stirred at room temperature for 15 min. Tetrabutylammonium bromide (0.9 mmol) was then added, and the mixture was stirred in the dark. After 72 h the mixture was diluted with CH_2Cl_2, filtered and concentrated. The crude product was purified by column chromatography (toluene/ acetone, 3:1) or (dichloromethane/methanol, 95:5 to 90:10) to afford the pure disaccharide.

Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (81)

Synthesized according to the general procedure for Tin-Mediated Glycosylation with Perbenzylated Glycosyl Bromide in 56% yield as a colorless oil.

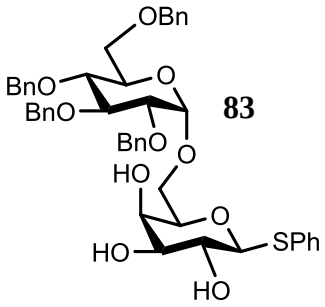


81

R_f 0.54 (CH_2Cl_2/MeOH 9:1). $[\alpha]_D$= +0.8 (c 0.3, $CHCl_3$). $\tilde{\upsilon}_{max}$ (film) 3318, 1454, 1114, 1026, 836, 530 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53 - 6.98 (m, 25H, C_6H_5), 4.86 (d, 1H, *J* = 10.9 Hz, OCH_2Ph), 4.74 (d, 1H, *J* = 10.9 Hz, OCH_2Ph), 4.69 (d, 1H, *J* = 10.9 Hz, OCH_2Ph), 4.67 (d, 1H, *J* = 3.3 Hz, H-1'), 4.66 (d, 1H, *J* = 10.9 Hz, OCH_2Ph), 4.54 (d, 1H, *J* = 12.1 Hz, OCH_2Ph), 4.51 (d, 1H, *J* = 12.1 Hz, OCH_2Ph), 4.43(d, 1H, *J* = 9.7 Hz, H-1), 4.39 (d, 1H, *J* = 9.7 Hz, OCH_2Ph), 4.38 (d, 1H, *J* = 9.7 Hz, OCH_2Ph), 4.02-3.79(m, 2H, H-6a, H-3'), 3.78-3.35 (m, 9H, H-2', H-5', H-4, H-6'ab, H-4', H-6b, H-5, H-3), 3.24 (dd, 1H, $J_{2\text{-}3}$ = 8.1 Hz, $J_{2\text{-}1}$ = 9 Hz, H-2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 138.2, 137.9, 137.8 (4C *ipso*-C_6H_5), 132.9 (*ipso*-C_6H_5), 132-127 (*o, m, p*- C_6H_5), 97.9 (C1'), 88.1 (C1), 82.1 (C3'), 79.7 (C2'), 77.6 (C4'), 77.5 (C3), 77.2 (C5'), 75.8 (OCH_2Ph) 75.1 (OCH_2Ph), 73.5 (2xOCH_2Ph), 72.1 (C5), 71.7 (C2), 70.5 (C4), 69.0 (C6'), 68.5 (C6) ppm. HRMS: calcd for $C_{46}H_{50}O_{10}S$ $[M + Na]^+$ 817.3022; found: 817.2997.

Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→6)-1-thio-β-D-galactopyranoside (83)

Synthesized according to the general procedure for Tin-Mediated Glycosylation with Perbenzylated Glycosyl Bromide in 52% yield as a colorless oil.

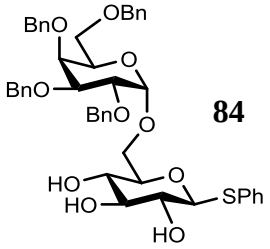


83

R_f 0.55 (CH_2Cl_2/ MeOH 9:1). $[\alpha]_D$= +0.6 (c 0.4; $CHCl_3$). $\tilde{\upsilon}_{max}$ (film) 3452, 1452, 1141, 1025, 881, 740, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 - 7.00 (m, 25H, C_6H_5), 4.87 (d, 1H, *J* = 11.7 Hz, OCH_2Ph), 4.86 (d, 1H, *J* = 3.7 Hz, H-1'), 4.75 (d, 1H, *J* = 10.7 Hz, OCH_2Ph), 4.74 (d, 1H, *J* = 10.7 Hz, OCH_2Ph), 4.70 (d, 1H, *J* = 11.6 Hz, OCH_2Ph), 4.61 (d, 1H, *J* = 11.9 Hz, OCH_2Ph), 4.52 (d, 1H, *J* = 12.1 Hz, OCH_2Ph), 4.42 (d, 1H, *J* = 9.7 Hz, H-1), 4.41 (d, 1H, *J* = 12.1 Hz, OCH_2Ph), 4.37 (d, 1H, *J* = 12.1 Hz, OCH_2Ph), 4.00 - 3.68 (m, 5H, H-4', H-3', H-6a, H-6b, H-5), 3.68-3.42 (m, 7H, H-2', H-2, H-5', H-6'ab, H-4, H-3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.6, 138.2, 137.9, 137.8 (4C *ipso*-C_6H_5), 132.5 (*ipso*- C_6H_5), 132-127 (*o*, *m*, *p*-C_6H_5), 98.0 (C1'), 88.9 (C1), 81.9 (C3'), 79.6 (C2'), 77.6 (C5), 77.2 (C4), 75.7 (OCH_2Ph), 75.1 (OCH_2Ph) 74.7 (C3), 73.5 (2xOCH_2Ph), 70.6 (C5), 70.2 (C2), 69.2 (C4'), 68.4 (C6'), 67.8 (C6) ppm. HRMS: calcd for $C_{46}H_{50}O_{10}S$ $[M + Na]^+$ 817.3022; found: 817.3004.

Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1→6)-1-thio-β-D-glucopyranoside (84)

Synthesized according to the general procedure for Tin-Mediated Glycosylation with Perbenzylated Glycosyl Bromide in 57% yield as a colorless oil.

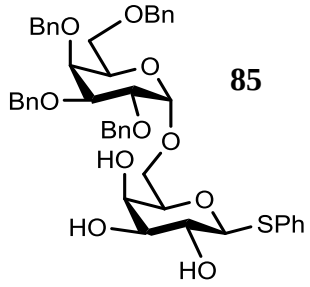


84

Colorless oil. R_f 0.56 (CH_2Cl_2/ MeOH 9:1). $[\alpha]_D$= +0.6 (c 0.5; $CHCl_3$). $\tilde{\upsilon}_{max}$ (film) 3372, 2880, 1454, 1345, 1217, 1113, 1090, 967, 834, 749, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47-7.11 (m, 25H, C_6H_5), 4.83 (d, 1H, *J* = 11.4 Hz, O*CH*$_2$Ph), 4.75 (d, 1H, *J* = 4.1 Hz, H-1'), 4.74 (d, 1H, *J* = 11.7 Hz, O*CH*$_2$Ph), 4.71 (d, 1H, *J* = 11.7 Hz, O*CH*$_2$Ph), 4.63 (d, 1H, *J* = 11.7 Hz, O*CH*$_2$Ph), 4.56 (d, 1H, *J* = 11.9 Hz, O*CH*$_2$Ph), 4.46 (d, 1H, *J* = 11.5 Hz, O*CH*$_2$Ph), 4.42 (d, 1H, *J* = 9.7 Hz, H-1), 4.38 (d, 1H, *J* = 11.8 Hz, O*CH*$_2$Ph), 4.31(d, 1H, *J* = 11.8 Hz, O*CH*$_2$Ph), 3.95 (dd, 1H, $J_{2'-1'}$ = 3.8 Hz, $J_{2'-3'}$ = 9.4 Hz, H-2'), 3.93-3.82 (m, 3H, H-5', H-4', H-6a), 3.79 (dd, 1H, $J_{3'-4'}$ = 3.5 Hz, $J_{3'-2'}$ = 9.6 Hz, H-3'), 3.51 (dd, 1H, J_{6b-5} = 4.7 Hz, J_{6b-a} = 10.3 Hz, H-6b), 3.47-3.35 (m, 5H, H-6'ab, H-4, H-5, H-3), 3.28-3.19 (m, 1H, H-2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 138.5, 138.1, 137.7 (4C *ipso*-C_6H_5), 132.8 (*ipso*-C_6H_5), 130-127 (*o*, *m*, *p*- C_6H_5), 98.5 (C1'), 87.7 (C1), 79.1 (C3'), 77.6 (C3), 77.3 (C4), 76.3 (C2'), 74.8 (2xO*C*H_2Ph) 73.7 (C5'), 73.5 (O*C*H_2Ph), 73.1 (O*C*H_2Ph), 72.0 (C5), 71.7 (C2), 69.7 (C4'), 69.1 (C6'), 68.9 (C6) ppm. HRMS: calcd for $C_{46}H_{50}O_{10}S$ $[M + Na]^+$ 817.3022; found: 817.3026.

Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1→6)-1-thio-β-D-galactopyranoside (85)

Synthesized according to the general procedure for Tin-Mediated Glycosylation with Perbenzylated Glycosyl Bromide in 52% yield as a colorless oil.



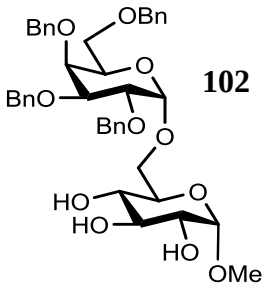
85

R_f 0.54 (CH_2Cl_2/ MeOH 9:1). $[\alpha]_D$= +0.9 (c 0.5, $CHCl_3$). $\tilde{\upsilon}_{max}$ (film) 3423, 1453, 1113, 1025, 868, 743, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 - 7.04 (m, 25H, C_6H_5), 4.88 (d, 1H, *J* = 3.7 Hz, H-1'), 4.83 (d, 1H, *J* = 11.4 Hz, O*CH*$_2$Ph), 4.74 (d, 1H, *J* = 11.8 Hz, O*CH*$_2$Ph), 4.70 (d, 1H, *J* = 11.8 Hz, O*CH*$_2$Ph), 4.64 (d, 1H, *J* = 11.7 Hz, O*CH*$_2$Ph), 4.61 (d, 1H, *J* = 11.8 Hz, O*CH*$_2$Ph), 4.46 (d, 1H, *J* = 11.4 Hz, O*CH*$_2$Ph), 4.39 (d, 1H, *J* = 9.5 Hz, H-1), 4.37 (d, 1H, *J* = 11.6 Hz, O*CH*$_2$Ph), 4.30 (d, 1H, *J* = 11.7 Hz, O*CH*$_2$Ph), 3.96 (dd, 1H, $J_{2'-1'}$ = 3.7 Hz, $J_{2'-3'}$ = 9.4 Hz, H-2'), 3.93-

3.82 (m, 4H, 6a-H, H-4', H-2, H-5'), 3.78 (dd, 1H, $J_{3'-4'}$ = 2.7 Hz, $J_{3'-2'}$ = 9.6 Hz, H-3'), 3.68 (dd, 1H, H-6b, J_{6b-5} = 5.3 Hz, J_{6b-a} = 10.9 Hz), 3.59-3.37 (m, 5H, H-6'ab, H-4, H-5, H-3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 138.6, 138.1, 137.9 (4C *ipso*-C_6H_5), 132.8 (*ipso*-C_6H_5), 133-127 (*o, m, p*- C_6H_5), 98.7 (C1'), 88.6 (C1), 78.9 (C3'), 77.2 (C2'), 76.2 (C4), 74.8 (C3), 74.7 (C5'), 73.8 (O*C*H_2Ph) 73.5 (O*C*H_2Ph), 72.9 (2xO*C*H_2Ph), 70.1 (C5), 69.7 (C2), 69.2 (C4'), 69.0 (C6'), 67.8 (C6) ppm. HRMS: calcd for $C_{46}H_{50}O_{10}S$ [M + Na] $^+$ 817.3022; found: 817.3012.

Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1→6)-α-D-glucopyranoside (102)

Synthesized according to the general procedure for Tin-Mediated Glycosylation with Perbenzylated Glycosyl Bromide in 52% yield as a colorless oil.



102

R_f =0.51 (CH_2Cl_2/ MeOH 9:1). $[\alpha]_D$= +5 (c 0.6; $CHCl_3$). $\tilde{\upsilon}_{max}$ (film) 3381, 1452, 1114, 1024, 965, 546 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 - 6.13 (m, 20H, C_6H_5), 4.85 (d, 1H, *J* = 11.5 Hz, O*CH*$_2$Ph), 4.77 (d, 1H, *J* = 12.0 Hz, O*CH*$_2$Ph), 4.73 (d, 1H, *J* = 11.5 Hz, O*CH*$_2$Ph), 4.71 (d, 1H, *J* = 2.5 Hz, H-1'), 4.65 (d, 1H, *J* = 11.6 Hz, O*CH*$_2$Ph), 4.64 (d, 1H, *J* = 3.5 Hz, H-1), 4.58 (d, 1H, *J* = 12.1 Hz, O*CH*$_2$Ph), 4.48 (d, 1H, *J* = 11.6 Hz, O*CH*$_2$Ph), 4.40 (d, 1H, *J* = 11.8 Hz, O*CH*$_2$Ph), 4.30 (d, 1H, *J* = 11.8 Hz, O*CH*$_2$Ph), 3.96 (dd, 1H, $J_{2'-1'}$ = 3.8 Hz, $J_{2'-3'}$ = 9.4 Hz, H-2'), 3.90-3.80 (m, 4H, H-2, H-3', H-3, H-6a), 3.67-3.58 (m, 2H, H-4', H-4), 3.52-3.31 (m, 5H, H-5, H-5', H-6'ab, H-6b), 3.31-3.27 (s, 3H, OC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 138.5, 138.3, 137.6 (4C *ipso*-C_6H_5), 133-127 (*o, m, p*- C_6H_5), 99.1 (C1), 98.8 (C1'), 79.1 (C3`), 76.2 (C2'), 74.8 (C3), 74.7 (C4), 74.3 (O*C*H_2Ph), 73.8 (O*C*H_2Ph) 73.6 (O*C*H_2Ph), 73.1 (O*C*H_2Ph), 72.3 (C5), 72.0 (C5'), 70.0 (C2), 69.4 (C4'), 69.3 (C6'), 69.2 (C6) ppm. HRMS: calcd for $C_{41}H_{48}O_{11}$ [M +Na] $^+$ 739.3094; found: 739.3082.

References

(1) Hakomori, S. *Curr. Opin. Immunol.* **1991**, *3*, 646–653.

(2) Gorelik, E.; Galili, U.; Raz, A. *Cancer Metastasis Rev.* **2001**, *20*, 245–277.

(3) Kato, K.; Ishiwa, A. *Trop. Med. Health* **2015**, *43*, 41–52.

(4) Yarema, K. J.; Bertozzi, C. R. *Curr. Opin. Chem. Biol.* **1998**, *2*, 49–61.

(5) Martin, A.; Arda, A.; Désiré, J.; Martin-Mingot, A.; Probst, N.; Sinaÿ, P.; Jiménez-Barbero, J.; Thibaudeau, S.; Blériot, Y. *Nat. Chem.* **2016**, *8*, 186–191.

(6) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.

(7) Koenigs, W.; Knorr, E. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 957–981.

(8) Lemieux, R. U.; Kullnig, R. K.; Bernstein, H. J.; Schneider, W. G. *J. Am. Chem. Soc.* **1958**, *80*, 6098–6105.

(9) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527–548.

(10) Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodong, U. *J. Chem. Soc., Chem. Commun.* **1988**, 823–825.

(11) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583–5584.

(12) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068–6070.

(13) Barrena, I.; Echarri, R.; Castillon, S. *Synlett* **1996**, 675–676.

(14) Veeneman, G. H.; Van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275–278.

(15) Nguyen, H. M.; Poole, J. L.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 414–417.

(16) Zhang, Z.; Ollmann, I. R.; Ye, X. S.; Wischnat, R.; Baasov, T.; Wong, C. H. *J. Am. Chem. Soc.* **1999**, *121*, 734–753.

(17) Wu, C.-Y.; Wong, C.-H. *Top. Curr. Chem.* **2011**, *301*, 223–252.

(18) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc.,*

Perkin Trans. 1 **1998**, 51–66.

(19) Jensen, H. H.; Pedersen, C. M.; Bols, M. *Chem. - Eur. J.* **2007**, *13*, 7576–7582.

(20) Boons, G.-J.; Geurtsen, R.; Holmes, D. *Tetrahedron Lett.* **1995**, *36*, 6325–6328.

(21) Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073–12074.

(22) Roy, R.; Andersson, F.; Letellier, M. *Tetrahedron Lett.* **1992**, *33*, 6053–6056.

(23) Pougny, J.-R.; Sinaÿ, P. *Tetrahedron Lett.* **1976**, *45*, 4073–4076.

(24) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed.* **1980**, *19*, 731–732.

(25) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405–2407.

(26) Levy, D. E.; Fugedi, P. *The Organic Chemistry of Sugars*; Taylor & Francis Group LCC, 2006.

(27) Fraser-Reid, B.; Tatsuta, K.; Thiem, J. *Glycoscience*; Springer, 2008.

(28) Pougny, J. R.; Jacquinet, J. C.; Nassr, M.; Duchet, D.; Milat, M. L.; Sinay, P. *J. Am. Chem. Soc.* **1977**, *99*, 6762–6763.

(29) Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Synlett* **2002**, 269–270.

(30) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179–205.

(31) Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N. *Carbohydr. Res.* **1973**, *27*, 55–61.

(32) Fugedi, P.; Garegg, P. J.; Lonn, H.; Norberg, T. *Glycoconj. J.* **1987**, *4*, 97–108.

(33) Lear, M. J.; Yoshimura, F.; Hirama, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 946–949.

(34) Dondoni, A.; Marra, A.; Massi, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1672–1676.

(35) Sato, S.; Mori, M.; Ito, Y.; Ogawa, T. *Carbohydr. Res.* **1986**, *155*, C6–C10.

(36) Garegg, P. J.; Henrichson, C.; Norberg, T. *Carbohydr. Res.* **1983**, *116*, 162–165.

(37) Van Cleve, J. W. *Carbohydr. Res.* **1979**, *70*, 161–164.

(38) Wiesner, K.; Jin, H.; Tsai, T. *Can. J. Chem.* **1984**, *62*, 1403–1405.

(39) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430–2434.

(40) Konradsson, P.; Mootoo, D. R.; Mcdevitt, R. E.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1990**, 270–272.

(41) Veeneman, G. H.; Van Leeuwen, S. H.; Van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334.

(42) Kihlberg, J. O.; Leigh, D. A.; Bundle, D. R. *J. Org. Chem.* **1990**, *55*, 2860–2863.

(43) Cura, P.; Aloui, M.; Kartha, K. P. R.; Field, R. A. *Synlett* **2000**, 1279–1280.

(44) Kartha, K. P. R.; Aloui, M.; Field, R. A. *Tetrahedron Lett.* **1996**, *37*, 5175–5178.

(45) Kartha, K. P. R.; Cura, P.; Aloui, M.; Readman, S. K.; Rutherford, T. J.; Field, R. a. *Tetrahedron: Asymmetry* **2000**, *11*, 581–593.

(46) Meijer, A.; Ellervik, U. *J. Org. Chem.* **2004**, *69*, 6249–6256.

(47) Fügedi, P.; Garegg, P. J. *Carbohydr. Res.* **1986**, *149*, C9–C12.

(48) Andersson, F. O.; Fúgedi, P.; Garegg, P. J.; Nashed, M. *Tetrahedron Lett.* **1986**, *27*, 3919–3922.

(49) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1990**, *202*, 225–238.

(50) Crich, D.; Smith, M. *Org. Lett.* **2000**, *2*, 4067–4069.

(51) Amatore, C.; Jutand, A.; Mallet, J.-M.; Meyer, G.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1990**, 718–719.

(52) Balavoine, G.; Gref, A.; Fischer, J.-C.; Lubineau, A. *Tetrahedron Lett.* **1990**, *31*, 5761–5764.

(53) Sinaÿ, P.; Amatore, C.; Mallet, J.-M.; Marra, A. *Synlett* **1990**, 572–574.

(54) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, *10*, 431–432.

(55) Rosenbrook, W.; Riley, D. A.; Lartey, P. A. *Tetrahedron Lett.* **1985**, *26*, 3–4.

(56) Suzuki, K.; Maeta, H.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3571–3574.

(57) Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379–1382.

(58) Nicolaou, K. C.; Chucholowski, A.; Dolle, R. E.; Randall, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, 1155–1156.

(59) Kunz, H.; Waldmann, H. *J. Chem. Soc., Chem. Commun.* **1985**, 638–640.

(60) Wessel, H. *Tetrahedron Lett.* **1990**, *31*, 6863–6866.

(61) Helferich, B.; Zirner, J. *Chem. Ber.* **1963**, *96*, 385–387.

(62) Zemplen, G.; Gerecs, A. *Chem. Ber.* **1930**, *63*, 2720–2729.

(63) Helferich, B.; Weis, K. *Chem. Ber.* **1956**, *89*, 314–321.

(64) Kronzer, F. J.; Schuerch, C. *Carbohydr. Res.* **1973**, *27*, 379–390.

(65) Fenger, T. H.; Madsen, R. *Eur. J. Org. Chem.* **2013**, 5923–5933.

(66) Demchenko, A. V. *Handbook of Chemical Glycosylation*; Wiley-VCH, 2008.

(67) Parrish, J. D.; Little, R. D. *Tetrahedron Lett.* **2001**, *42*, 7371–7374.

(68) Shoda, S. I.; Moteki, M.; Izumi, R.; Noguchi, M. *Tetrahedron Lett.* **2004**, *45*, 8847–8848.

(69) Kumar, R.; Tiwari, P.; Maulik, P. R.; Misra, A. K. *Eur. J. Org. Chem.* **2006**, 74–79.

(70) Roth, W.; Pigman, W. *Methods Carbohydr. Chem.* **1963**, *2*, 405–408.

(71) Meloncelli, P. J.; Martin, A. D.; Lowary, T. L. *Carbohydr. Res.* **2009**, *344*, 1110–1122.

(72) Helferich, B.; Gootz, R. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 2788–2792.

(73) Caputo, R.; Kunz, H.; Mastroianni, D.; Palumbo, G.; Pedatella, S.; Solla, F. *Eur. J. Org. Chem.* **1999**, 3147–3150.

(74) Tanaka, H.; Sakamoto, H.; Sano, A.; Nakamura, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **1999**, 1259–1260.

(75) Schmid, U.; Waldmann, H. *Tetrahedron Lett.* **1996**, *37*, 3837–3840.

(76) van Well, R. M.; Kärkkäinen, T. S.; Kartha, K. P. R.; Field, R. A. *Carbohydr. Res.* **2006**, *341*, 1391–1397.

(77) Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *Tetrahedron Lett.* **2003**, *44*, 7863–7866.

(78) Thiem, J.; Meyer, B. *Chem. Ber.* **1980**, *113*, 3075–3085.

(79) Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 61–69.

(80) Gervay, J.; Nguyen, T. N.; Hadd, M. J. *Carbohydr. Res.* **1997**, *300*, 119–125.

(81) Dwek, R. *Chem. Rev.* **1996**, *96*, 683–720.

(82) Hakomori, S. *Acta Anat.* **1998**, *161*, 79–90.

(83) Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. *Science* **2001**, *291*, 2370–2376.

(84) Linhardt, R.; Kuberan, B. *Curr. Org. Chem.* **2000**, *4*, 653–677.

(85) Suzuki, E.; Tanaka, A. K.; Toledo, M. S.; Levery, S. B.; Straus, A. H.; Takahashi, H. K. *Biochim. Biophys. Acta* **2008**, *1780*, 362–369.

(86) Demchenko, A. V. *Curr. Org. Chem.* **2003**, *7*, 35–79.

(87) Wolfrom, M.; Pittet, A.; Gillam, I. *Proc. Natl. Acad. Sci. U. S. A.* **1961**, *47*, 700–705.

(88) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N.; Alexey, V. *Carbohydr. Res.* **1991**, *212*, 77–91.

(89) Brigl, P.; Keppler, H. *Ber. Dtsch. Chem. Ges.* **1926**, *59*, 1588–1591.

(90) Paulsen, H. *Angew. Chem., Int. Ed.* **1982**, *21*, 155–173.

(91) Kochetkov, N. K.; Klimov, E. M.; Malysheva, N. N. *Tetrahedron Lett.* **1989**, *30*, 5459–5462.

(92) Eby, R.; Schuerch, C. *Carbohydr. Res.* **1974**, *34*, 79–90.

(93) Fletcher, G.; Ishikawa, T. *J. Org. Chem.* **1969**, *34*, 563–571.

(94) Boeckel, C.; Beetz, T.; Aelst, S. *Tetrahedron* **1984**, *40*, 4097–4107.

(95) Fei, C. P.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 849–852.

(96) Houdier, S.; Vottero, P. J. A. *Carbohydr. Res.* **1992**, *232*, 349–352.

(97) Fukase, K.; Nakai, Y.; Kanoh, T.; Kusumoto, S. *Synlett* **1998**, 84–86.

(98) Fukase, K.; Nakai, Y.; Egusa, K.; Porco, J. A.; Kusumoto, S. *Synlett* **1999**, 1074–1078.

(99) Lucas, T.; Schuerch, C. *Carbohydr. Res.* **1975**, *39*, 39–45.

(100) Nakahara, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2731–2734.

(101) Demchenko, A. V; Rousson, E.; Boons, G. *Tetrahedron Lett.* **1999**, *40*, 6523–6526.

(102) Gerbst, A. G.; Ustuzhanina, N. E.; Grachev, A. A.; Tsvetkov, D. E.; Khatuntseva, A.; Nifant, N. E. *Mendeleev Commun.* **1999**, *9*, 114–116.

(103) Zuurmond, H. M.; Laan, S. C. Van Der; Jacques, H.; Boom, V. *Carbohydr. Res.* **1991**, *215*, c1–c3.

(104) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merritt, J.; Rao, C.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927–942.

(105) Wulff, G.; Rohle, G. *Angew. Chem., Int. Ed.* **1974**, *13*, 157–170.

(106) Demchenko, A. V.; Stauch, T.; Boons, G. J. *Synlett* **1997**, 818–820.

(107) Sinay, P.; Ernst, B.; Hart, G. *Carbohydrates in Chemistry and Biology*; Wiley-VCH Verlag GmbH, 2000.

(108) Sinay, P. *Pure Appl. Chem.* **1978**, *50*, 1437–1452.

(109) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819–6825.

(110) Hashimoto, S.; Sakamoto, H.; Honda, T.; Abe, H.; Nakamura, S.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 8969–8972.

(111) Kronzer, F. J.; Schuerch, C. *Carbohydr. Res.* **1974**, *34*, 71–78.

(112) Shimizu, H.; Ito, Y.; Ogawa, T. *Synlett* **1994**, 535–536.

(113) Schmidt, R. R.; Rücker, E. *Tetrahedron Lett.* **1980**, *21*, 1421–1424.

(114) Dohi, H.; Nishida, Y.; Tanaka, H.; Kobayashi, K. *Synlett* **2001**, 1446–1448.

(115) Sasaki, M.; Gama, Y.; Yasumoto, M.; Ishigami, Y. *Tetrahedron* **1990**, *31*, 6549–6552.

(116) Lockhoff, H. P.; Paulsen, H. *Chem. Ber.* **1981**, *114*, 3102–3114.

(117) Eby, R.; Schuerch, C. *Carbohydr. Res.* **1982**, *102*, 131–138.

(118) Srivastava, V. K.; Schuerch, C. *J. Org. Chem.* **1981**, *46*, 1121–1126.

(119) Lindhorst, T. . *Essentials of Carbohydrate Chemistry and Biochemistry*; Wiley-VCH, 2007.

(120) Chernyak, A.; Oscarson, S.; Turek, D. *Carbohydr. Res.* **2000**, *329*, 309–316.

(121) Baeschlin, D. K.; Charbonneau, V.; Green, L. G.; Ley, S. V; Lücking, U.; Walther, E. *Angew. Chem., Int. Ed.* **1998**, *37*, 3423–3428.

(122) Lemieux, U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4069–4075.

(123) Filser, C.; Kowalczyk, D.; Jones, C.; Wild, M. K.; Ipe, U.; Vestweber, D.; Kunz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2108–2111.

(124) Coteron, J. M.; Singh, K.; Asensio, J. L.; Dalda-Dominguez, M.; Ferndndez-Mayoralas, A.; Jimenez-Barbero, J.; Martin-Lomas, M.; Abad-Rodriguez, J.; Nieto-Sampedro, M. *J. Org. Chem.* **1995**, *60*, 1502–1519.

(125) Wotovic, A.; Jacquinet, J.-C.; Sinaÿ, P. *Carbohydr. Res.* **1990**, *205*, 235–245.

(126) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 2400–2412.

(127) Posner, G. H.; Bull, D. S. *Tetrahedron Lett.* **1996**, *37*, 6279–6282.

(128) Uchiro, H.; Mukaiyama, T. *Chem. Lett.* **1996**, *25*, 79–80.

(129) Nguyen, H. M.; Chen, Y.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 8766–8772.

(130) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212–235.

(131) Schmidt, R. R.; Klotz, W.; Tsvetkov, Y. *Liebigs Ann. Chem.* **1992**, 361–370.

(132) Wegmann, B.; Schmidt, R. R. *J. Carbohydr. Chem.* **1987**, *6*, 357–375.

(133) Schmidt, R. R.; Toepfer, A. *Tetrahedron Lett.* **1991**, *32*, 3353–3356.

(134) Lassaletta, J. M.; Carlsson, K.; Garegg, P. J.; Schmidt, R. R. *J. Org. Chem.* **1996**, *61*, 6873–6880.

(135) Boons, G.-J.; Bowers, S.; Coeb, D. M. *Tetrahedron Lett.* **1997**, *38*, 3773–3776.

(136) Ye, X. S.; Wong, C. H. *J. Org. Chem.* **2000**, *65*, 2410–2431.

(137) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1988**, *29*, 1061–1064.

(138) Boons, G.-J.; Stauch, T. *Synlett* **1996**, 906–908.

(139) Wang, W.; Kong, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1247–1250.

(140) Wang, W.; Kong, F. *J. Org. Chem.* **1998**, *63*, 5744–5745.

(141) Zdorovenko, E. L.; Zatonsky, G. V; Zdorovenko, G. M.; Pasichnyk, A.; Shashkov, A. S.; Knirel, A. *Carbohydr. Res.* **2001**, *336*, 329–336.

(142) Reddy, G. V.; Jain, R. K.; Locke, R. D.; Matta, K. L. *Carbohydr. Res.* **1996**, *280*, 261–276.

(143) Kong, F. Z. *Curr. Org. Chem.* **2003**, *7*, 841–865.

(144) Kartha, R. K. P.; Kiso, M.; Hasegawa, A.; Jennings, H. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 3023–3026.

(145) Hasegawa, A.; Ohki, H.; Nagahama, T.; Ishida, H.; Kiso, M. *Carbohydr. Res.* **1991**, *212*, 277–281.

(146) Matwiejuk, M.; Thiem, J. *Eur. J. Org. Chem.* **2011**, 5860–5878.

(147) Matwiejuk, M.; Thiem, J. *Chem. Commun.* **2011**, *47*, 8379–8381.

(148) Boettcher, S.; Matwiejuk, M.; Thiem, J. *Beilstein J. Org. Chem.* **2012**, *8*, 413–420.

(149) Pelletier, G.; Zwicker, A.; Allen, C. L.; Schepartz, A.; Miller, S. J. *J. Am. Chem. Soc.* **2016**, *138*, 3175–3182.

(150) Angyal, S. J. *Carbohydr. Res.* **1990**, *200*, 181–188.

(151) Evtushenko, E. V. *Synth. Commun.* **2006**, *36*, 1593–1599.

(152) Eby, R.; Schuerch, C. *Carbohydr. Res.* **1982**, *100*, C41–C43.

(153) Schuerch, C.; Eby, R.; Webster, K. *Carbohydr. Res.* **1984**, *129*, 111–120.

(154) Hanessian, S.; Kagotani, M. *Carbohydr. Res.* **1990**, *202*, 67–79.

(155) Gangadharmath, U. B.; Demchenko, A. V. *Synlett* **2004**, 2191–2193.

(156) Evtushenko, E. V. *J. Carbohydr. Chem.* **2010**, *29*, 369–378.

(157) Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 17–142.

(158) Nashed, M. A.; Anderson, L. *Tetrahedron Lett.* **1976**, *39*, 3503–3506.

(159) Munavu, R. *J. Org. Chem.* **1976**, *41*, 1832–1836.

(160) Ogawa, T.; Matsui, M. *Carbohydr. Res.* **1976**, *51*, C13–C18.

(161) Tsuda, Y.; Haque, M. E.; Yoshimoto, K. *Chem. Pharm. Bull.* **1983**, *31*, 1612–1624.

(162) Ogawa, T.; Matsui, M.; Katano, K. *Carbohydr. Res.* **1978**, *64*, C3–C9.

(163) Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *Carbohydr. Res.* **1990**, *203*, 296–301.

(164) Murase, T.; Kartha, K. P. R.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1989**, *195*, 134–137.

(165) David, S.; Thieffry, A.; Veyrieres, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1796–1801.

(166) Garegg, P. J.; Maloisel; Oscarson, S. *Synthesis* **1995**, 409–414.

(167) Kaji, E.; Harita, N. *Tetrahedron Lett.* **2000**, *41*, 53–56.

(168) Haque, M. E.; Kikuchi, T.; Yoshimoto, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1985**, *33*, 2243–2255.

(169) Leigh, D. A.; Martin, R. P.; Smart, J. P.; Truscello, A. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1373–1374.

(170) Kaji, E.; Shibayama, K.; In, K. *Tetrahedron Lett.* **2003**, *44*, 4881–4885.

(171) Ohno, M.; Nagashima, N. *Chem. Pharm. Bull.* **1991**, *39*, 1972–1982.

(172) Maggi, A.; Madsen, R. *Eur. J. Org. Chem.* **2013**, 2683–2691.

(173) Muramatsu, W.; Yoshimatsu, H. *Adv. Synth. Catal.* **2013**, *355*, 2518–2524.

(174) Oshima, K.; Aoyama, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2315–2316.

(175) Gouliaras, C.; Lee, D.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 13926–13929.

(176) Jin, S.; Cheng, Y.; Reid, S.; Li, M.; Wang, B. *Med. Res. Rev.* **2010**, *30*, 171–257.

(177) Greene, T. W.; Wuts, P. G. M. *Greene's Protective Groups in Organic Synthesis*; Wiley-Interscience, 2007.

(178) Kaji, E.; Nishino, T.; Ishige, K.; Ohya, Y.; Shirai, Y. *Tetrahedron Lett.* **2010**, *51*, 1570–1573.

(179) Kaji, E.; Makino, K.; Yamamoto, D.; Shirahata, T.; Murai, R.; Ohya, Y.; Nishino, T. *Heterocycles* **2012**, *84*, 1123–1140.

(180) Janczuk, A. J.; Zhang, W.; Andreana, P. R.; Warrick, J.; Wang, P. G. *Carbohydr. Res.* **2002**, *337*, 1247–1259.

(181) Kowalczyk, R.; Harris, P. W. R.; Dunbar, R. P.; Brimble, M. A. *Synthesis* **2009**, 2210–2222.

(182) Dinkelaar, J.; Jong, A. R. de; Meer, R. van; Somers, M.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 4982–4991.

(183) Weygand, F. von; Ziemann, H. *Liebigs Ann. Chem.* **1962**, 179–198.

(184) Motavi, M. .; Marcussen, J.; Møller, B. . *J. Carbohydr. Chem.* **1995**, *14*, 1279–1294.

(185) Grayson, E. J.; Ward, S. J.; Hall, A. L.; Rendle, P. M.; Gamblin, D. P.; Batsanov, A. S.; Davis, B. G. *J. Org. Chem.* **2005**, *70*, 9740–9754.

(186) Wessels, H.-P.; Bundle, D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2251–2260.

(187) Kobashi, Y.; Mukaiyama, T. *Chem. Lett.* **2004**, *33*, 10–11.

(188) Kobashi, Y.; Mukaiyama, T. *Chem. Lett.* **2004**, *33*, 874–875.

(189) Meloncelli, P. J.; Williams, T. M.; Hartmann, P. E.; Stick, R. V. *Carbohydr. Res.* **2007**, *342*, 1793–1804.

(190) Glaudemans, C.; Fletcher, H. *J. Org. Chem.* **1963**, *28*, 3004–3006.

(191) Muramatsu, W.; Takemoto, Y. *J. Org. Chem.* **2013**, *78*, 2336–2345.

(192) Muramatsu, W. *J. Org. Chem.* **2012**, *77*, 8083–8091.

(193) Kartha, K. P. R.; Aloui, M.; Field, R. A. F. *Tetrahedron Lett.* **1996**, *37*, 8807–8810.

(194) Urban, F. J.; Moore, B. S.; Breitenbach, R. *Tetrahedron Lett.* **1990**, *31*, 4421–4424.

(195) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687–2704.

(196) Schuerch, C.; Rachman, E. *Carbohydr. Res.* **1978**, *67*, 147–161.

(197) Ekholm, F.; Poláková, M.; Pawłowicz, A.; Leino, R. *Synthesis* **2009**, 567–576.

(198) Pedretti, V.; Veyrières, A.; Sinaÿ, P. *Tetrahedron* **1990**, *46*, 77–88.

(199) Bredenkamp, M. W. *S. Afr. J. Chem.* **1995**, *48*, 154–156.

(200) Hernández-Torres, J. M.; Liew, S.-T.; Achkar, J.; Wei, A. *Synthesis* **2002**, 487–490.

(201) Macmillan, D.; Daines, A. M.; Bayrhuber, M.; Flitsch, S. L. *Org. Lett.* **2002**, *4*, 1467–1470.

(202) Clausen, M. H.; Jørgensen, M. R.; Thorsen, J.; Madsen, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 543–551.

(203) Li, T.; Wen, L.; Williams, A.; Wu, B.; Li, L.; Qu, J.; Meisner, J.; Xiao, Z.; Fang, J.; Wang, P. G. *Bioorg. Med. Chem.* **2014**, *22*, 1139–1147.

(204) Rye, C. S.; Withers, S. G. *J. Am. Chem. Soc.* **2002**, *124*, 9756–9767.

(205) Dong, H.; Zhou, Y.; Pan, X.; Cui, F.; Liu, W.; Liu, J.; Ramström, O. *J. Org. Chem.* **2012**, *77*, 1457–1467.

(206) Zhou, Y.; Li, J.; Zhan, Y.; Pei, Z.; Dong, H. *Tetrahedron* **2013**, *69*, 2693–2700.

(207) Hanessian, S.; Lou, B. *Chem. Rev.* **2000**, *100*, 4443–4463.

(208) Davis, B. G.; Wood, S. D.; Maughan, M. A. *Can. J. Chem.* **2002**, *80*, 555–558.

(209) Gudmundsdottir, A. V; Nitz, M. *Org. Lett.* **2008**, *10*, 3461–3463.

(210) Wilkinson, S. M.; Liew, C. W.; Mackay, J. P.; Saleh, H. M.; Withers, S. G.; McLeod, M. D. *Org Lett.* **2008**, *10*, 1585–1588.

(211) Williams, R. J.; Paul, C. E.; Nitz, M. *Carbohydr. Res.* **2014**, *386*, 73–77.

(212) Pruckmayr, G.; Wu, T. K. *Macromolecules* **1978**, *11*, 265–270.

(213) Crick, D. C.; Li, K.; Kurosu, M. *Org. Lett.* **2009**, *11*, 2393–2396.

(214) Murakami, T.; Sato, Y.; Shibakami, M. *Carbohydr. Res.* **2008**, *343*, 1297–1308.

(215) Lee, D.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 3724–3727.

(216) Lanz, G.; Madsen, R. *Eur. J. Org. Chem.* **2016**, 3119–3125.

(217) Karimi, B.; Zamani, A.; Zareyee, D. *Tetrahedron Lett.* **2004**, *45*, 9139–9141.

(218) Chan, L.; Taylor, M. S. *Org. Lett.* **2011**, *13*, 3090–3093.

(219) Williams, J. M.; Richardson, A. C. *Tetrahedron* **1967**, *23*, 1369–1378.

(220) Twibanire, J. D. A. K.; Grindley, T. B. *Org. Lett.* **2011**, *13*, 2988–2991.

(221) Kartha, K. P. R. P. R.; Field, R. A. *Tetrahedron* **1997**, *53*, 11753–11766.

(222) Bourhim, A.; Czernecki, S.; Krausz, P. *J. Carbohydr. Chem.* **1993**, *12*, 853–863.

(223) Williams, J. M.; O'Brien, E.; Bullock, C.; Batey, J. *Carbohydr. Res.* **1975**, *43*, 43–50.

(224) Demizu, Y.; Kubo, Y.; Miyoshi, H.; Maki, T.; Matsumura, Y.; Moriyama, N.; Onomura, O. *Org. Lett.* **2008**, *10*, 5075–5077.

(225) Chang, C.-F. *Carbohydrates - Comprehensive Studies on Glycobiology and Glycotechnology*; InTech, 2012.

(226) Bernstein, S.; Conrow, R. *J. Org. Chem.* **1971**, *36*, 863–870.

(227) Yamada, H.; Hayashi, T. *Carbohydr. Res.* **2002**, *337*, 581–585.

(228) Evtushenko, E. V. *Carbohydr. Res.* **2012**, *359*, 111–119.

(229) Osztrovszky, G. Studies and Applications of Metals for the Synthesis of Carbinols, Amides and Carbohydrates, 2011.

(230) Motawia, M. S.; Olsen, C. E.; Denyer, K.; Smith, A. M.; Møller, B. L. *Carbohydr. Res.* **2001**, *330*, 309–318.

(231) Motawia, M. S.; Olsen, C. E.; Enevoldsen, K.; Marcussen, J.; Møller, B. L. *Carbohydr. Res.* **1995**, *277*, 109–123.

(232) Tiwari, P.; Misra, A. K. *J. Org. Chem.* **2006**, *71*, 2911–2913.

(233) Weng, S.-S.; Lin, Y.-D.; Chen, C.-T. *Org. Lett.* **2006**, *8*, 5633–5636.

(234) Timmons, S. C.; Jakeman, D. L. *Org. Lett.* **2007**, *9*, 1227–1230.

(235) Yoneda, Y.; Krainz, K.; Liebner, F.; Potthast, A.; Rosenau, T.; Karakawa, M.; Nakatsubo, F. *Eur. J. Org. Chem.* **2008**, 475–484.

(236) Malik, S.; Dixit, V. A.; Bharatam, P. V.; Kartha, K. P. R. *Carbohydr. Res.* **2010**, *345*, 559–564.

(237) Roslund, M. U.; Aitio, O.; Wärna, J.; Maaheimo, H.; Murzin, D. Y.; Leino, R.; Wärnå, J.; Maaheimo, H.; Murzin, D. Y.; Leino, R. *J. Am. Chem. Soc.* **2008**, *130*, 8769–8772.

(238) Klein, T.; Abgottspon, D.; Wittwer, M.; Rabbani, S.; Herold, J.; Jiang, X.; Kleeb, S.; Lüthi, C.; Scharenberg, M.; Bezençon, J.; Gubler, E.; Pang, L.; Smiesko, M.; Cutting, B.; Schwardt, O.; Ernst, B. *J. Med. Chem.* **2010**, *53*, 8627–8641.

(239) Encinas, L.; Chiara, J. L. *J. Comb. Chem.* **2008**, *10*, 361–363.

(240) Bianchi, A.; Bernardi, A. *J. Org. Chem.* **2006**, *71*, 4565–4577.

(241) de la Fuente, J. M.; Penadés, S. *Tetrahedron: Asymmetry* **2002**, *13*, 1879–1888.

(242) Zeng, J.; Vedachalam, S.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2011**, *13*, 42–45.

(243) Lee, Y. J.; Baek, J. Y.; Lee, B.-Y.; Kang, S. S.; Park, H.-S.; Jeon, H. B.; Kim, K. S. *Carbohydr. Res.* **2006**, *341*, 1708–1716.

(244) Han, Z.; Achilonu, M. C.; Kendrekar, P. S.; Joubert, E.; Ferreira, D.; Bonnet, S. L.; Van Der Westhuizen, J. H. *J. Nat. Prod.* **2014**, *77*, 583–588.

(245) Van Dongen, S. F. M.; Nallani, M.; Cornelissen, J. J. L. M.; Nolte, R. J. M.; Van Hest, J. C. M. *Chem. - Eur. J.* **2009**, *15*, 1107–1114.

(246) McGeary, R. P.; Rasoul Amini, S.; Tang, V. W. S.; Toth, I. *J. Org. Chem.* **2004**, *69*, 2727–2730.

(247) Liguori, A.; Procopio, A.; Romeo, G.; Sindona, G.; Uccella, N. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1783.

Appendix

Niedbal, D. A.; Madsen, R. “Halide-mediated regioselective 6-*O*-glycosylation of unprotected hexopyranosides with perbenzylated glycosyl bromide donors” *Tetrahedron* **2016**, 72, 415-419.

Tetrahedron 72 (2016) 415–419

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Halide-mediated regioselective 6-*O*-glycosylation of unprotected hexopyranosides with perbenzylated glycosyl bromide donors

Dominika Alina Niedbal, Robert Madsen *

Department of Chemistry, Technical University of Denmark, 2800 Kgs. Lyngby, Denmark

ARTICLE INFO

Article history:
Received 22 September 2015
Received in revised form 10 November 2015
Accepted 24 November 2015
Available online 27 November 2015

Keywords:
Glycosylation
Glycosyl bromide
Regioselectivity
Stannane
Stereoselectivity

ABSTRACT

The regio- and stereoselective glycosylation at the 6-position in 2,3,4,6-unprotected hexopyranosides has been investigated with dibutyltin oxide as the directing agent. Perbenzylated hexopyranosyl bromides were employed as the donors and the glycosylations were promoted by tetrabutylammonium bromide. The couplings were completely selective for both glucose and galactose donors and acceptors as long as the stannylene acetal of the acceptor was soluble in dichloromethane. This gave rise to a number of 1,2-cis-linked disaccharides in reasonable yields. Mannose donors and acceptors, on the other hand, did not react in the glycosylation under these conditions.

1. Introduction

The chemical synthesis of oligosaccharides lies at the cornerstone of carbohydrate chemistry due to the immense biological importance of glycans. The area has experienced significant progress over the past three decades with the development of new effective glycosyl donors, promoters and coupling strategies.[1] This has made it possible to synthesize rather large oligosaccharides with more than 20 monosaccharides where each glycosidic linkage is formed with excellent stereocontrol and in good yield.[2] However, the regioselectivity is still controlled by the use of partially protected glycosyl acceptors containing one free hydroxy group. These acceptors are prepared through several protecting group manipulations which add a considerable number of steps to the synthesis of a target molecule. Accordingly, the chemical synthesis of oligosaccharides from monosaccharides is still quite a time-consuming event due to the preparation of building blocks and the transformation of protecting groups.

As a result, there is an increasing interest in the development of regioselective glycosylations with 2,3,4,6-unprotected glycosyl acceptors.[3] Although these acceptors contain both a primary and several secondary hydroxy groups, the direct glycosylation of the primary hydroxy group generally gives poor regioselectivity.[4] Therefore, several directing agents based on tin and boron have been developed in order to steer the donor to only one hydroxy group. These reagents can mediate very regioselective glycosylations to either the primary hydroxy group or to the most reactive secondary alcohol.

Bu_2SnO has been employed in the glycosylation of a number of unprotected β-galacto- and β-glucopyranosides to afford the (1 → 6)-linked disaccharides in good yield.[5] These reactions are believed to proceed through the 4,6-stannylene acetal of the acceptor which enhances the reactivity of the 6-position. On the contrary, Ph_2SnCl_2 mediates the selective glycosylation of the 3-position in 2,3,4,6-unprotected mannosides, glucosides and galactosides.[6] The same selectivity is achieved by transient masking of the 4- and the 6-position with boronic acids in glucosides and galactosides[7] while fully unprotected glucose under these conditions gives glycosylation at position 6 due to temporary blocking of position 1, 2, 3 and 5.[8] Regioselective glycosylation at position 3 in mannosides and galactosides can also be achieved in a borinic acid-catalyzed protocol although protection of position 6 is necessary in this case.[9,10]

However, most of these procedures employ the Koenigs–Knorr glycosylation with peracylated glycosyl bromides and various silver salts as promoters giving rise to the 1,2-trans coupling products. In a few cases peracylated thioglycosides have been used as donors with DMTST[5c] and NIS/Lewis acid[7a,8] as promoters. In addition, the halide ion-catalyzed glycosylation[11] has been utilized with tin reagents for glycosylating methyl β-D-galactopyranoside at position 6 (with perbenzylated glucosyl bromide)[5c] and methyl β-lactoside at position 6′ (with perbenzylated galactosyl bromide).[5d] The latter

* Corresponding author. Tel.: +45 4525 2151; fax: +45 4588 3136; e-mail address: rm@kemi.dtu.dk (R. Madsen).

http://dx.doi.org/10.1016/j.tet.2015.11.059
0040-4020/

two examples are interesting since a cheap glycosylation method is employed and the product is obtained with a 1,2-cis relationship. However, the scope and limitations of this approach have not been thoroughly explored and we therefore decided to investigate the halide ion-catalyzed glycosylation with a range of donors and acceptors under different conditions. Herein, we report full details of the bromide-mediated glycosylation of the 6-position in 2,3,4,6-unprotected hexopyranosides in the presence of Bu_2SnO.

2. Results and discussion

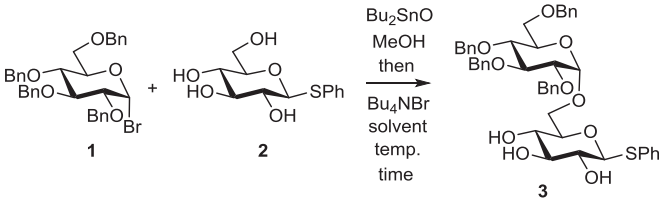
Unprotected phenyl 1-thioglycopyranosides were selected as acceptors for these studies in line with our earlier work[5a,7a] since the regioselective glycosylation would then provide a straightforward route to a number of thioglycoside building blocks that are useful glycosyl donors. For optimizing the reaction conditions both a glucose donor and a glucose acceptor was employed. Tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**1**) was prepared from the corresponding lactol with oxalyl bromide in dichloromethane.[12] Although, bromide **1** in some references has been described as highly unstable, the compound can be purified by silica gel flash chromatography with ethyl acetate/heptane and stored at −15 °C for months.

The regioselective coupling of **1** to phenyl 1-thio-β-D-glucopyranoside (**2**) was performed by treating the latter with 1 equiv of Bu_2SnO in methanol followed by removal of the solvent and drying under high vacuum. The resulting stannylene acceptor complex was then dissolved in dichloromethane with 1.8 equiv of donor **1** and 1.8 equiv of tetra-*n*-butylammonium bromide. After stirring overnight at room temperature the (1 → 6)-linked disaccharide **3** was isolated in 40% yield as the pure α anomer with unreacted donor and acceptor as the only remaining compounds in the mixture (Table 1, entry 1). This indicates that the desired reaction is very stereo- and regioselective under these conditions. However, it is also a rather slow transformation and the coupling was therefore subjected to a further optimization.

The reaction in THF, acetonitrile and trichloroethane produced slightly lower yields than in dichloromethane (entries 2–4). Increasing the reaction temperature gave better conversion in THF while no improvements were observed in acetonitrile and trichloroethane (entries 5–7). However, in THF and acetonitrile the product **3** was obtained as an α/β mixture with a ratio of about 10:1, which renders these conditions unattractive. No conversion occurred in DMF while the stannylene acetal complex was not fully soluble in diethyl ether, dioxane and toluene and therefore only produced a 10–15% yield of **3** in these solvents (results not shown).

Consequently, attention shifted back to dichloromethane where the reaction was repeated in the presence of 4 Å molecular sieves (MS)[13] which increased the yield to 46% (entry 8). When this coupling was performed in the absence of Bu_2SnO the yield dropped to 17% and several byproducts were now clearly visible by TLC (entry 9). This experiment shows that the stannylene acetal is essential to form exclusively the (1 → 6)-linked glycosylation product. Higher or lower temperature gave lower yield in the presence of Bu_2SnO (entries 10 and 11) and room temperature was therefore selected for general use. Interestingly, the amount of Bu_2SnO could be lowered to 10% and the disaccharide **3** was still obtained in a modest yield (entries 12 and 13). The acceptor **2** was not fully soluble in dichloromethane upon pretreatment with only a catalytic amount of Bu_2SnO. This may account for the slightly lower yield under these conditions which is about 15% higher than in the absence of Bu_2SnO (entries 9, 12 and 13). Attempts to replace Bu_2SnO with 10% of Bu_2SnCl_2, Ph_2SnCl_2 or Me_2SnCl_2 gave less than 25% yield of **3** (results not shown). Decomposition of the donor occurred when molecular sieves were replaced with a base such as collidine or lutidine. Replacing the promoter with the stronger activator I_2/DDQ[14] gave essentially the same yield as with Bu_4NBr, but now as a 2:3 α/β mixture (entry 14).

Table 1
Optimization of the regioselective glycosylation



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	CH_2Cl_2	20	18	40
2	THF	20	18	35
3	CH_3CN	20	18	30
4	CH_3CCl_3	20	18	25
5	THF	40	18	45[b]
6	CH_3CN	40	18	30[b]
7	CH_3CCl_3	40	18	18
8[c]	CH_2Cl_2	20	18	46
9[c,d]	CH_2Cl_2	20	18	17
10[c]	CH_2Cl_2	40	8	10
11[c]	CH_2Cl_2	0	18	8
12[c,e]	CH_2Cl_2	20	18	35
13[e]	CH_2Cl_2	20	18	30
14[c,f]	CH_2Cl_2	20	18	48[b]
15[c]	CH_2Cl_2	20	24	50
16[c]	CH_2Cl_2	20	72	56
17[c,e]	CH_2Cl_2	20	24	40
18[c,e]	CH_2Cl_2	20	72	46
19[c,g]	CH_2Cl_2	20	72	45

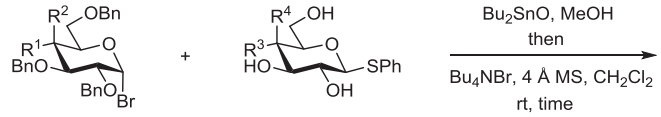
[a] Isolated yield.
[b] Product obtained as an α/β mixture.
[c] 4 Å molecular sieves were also added in the glycosylation.
[d] Reaction performed in the absence of Bu_2SnO.
[e] With 10% of Bu_2SnO.
[f] Bu_4NBr was replaced with I_2/DDQ.
[g] With 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride instead of **1**.

In all these experiments with Bu_2SnO the remaining material in the mixture was unreacted donor and acceptor. Therefore, it was decided to extend the reaction time which produced **3** in 50% yield after 24 h and 56% after 72 h (entries 15 and 16). Both yields were lowered by 10% when only a catalytic amount of Bu_2SnO was employed (entries 17 and 18). Replacing bromide **1** with the corresponding glycosyl chloride also gave a lower yield of **3** due to a slower conversion (entry 19).

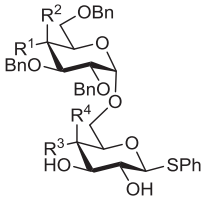
The optimized conditions were then applied for coupling between **1** and galactose acceptor **4** which produced disaccharide **5** in 52% yield after 24 h and 58% after 72 h (Table 2, entries 1 and 2). Again, a decrease of about 10% was observed when the glycosylation was performed with only a catalytic amount of Bu_2SnO (entries 3 and 4). Galactose donor **6** was also prepared and coupled to acceptors **2** and **4** to afford disaccharides **7** and **8**, respectively. The reactions were performed with both stoichiometric and catalytic amounts of Bu_2SnO and the yields were essentially the same as obtained with glucose donor **1** (entries 5–12). All the glycosylations under the optimized conditions gave exclusively the α-linked disaccharides and none of the β-isomers were detected. The regioselectivity was confirmed by HMBC correlations between H-1′ and C-6 in the products.

It was attempted to perform the same couplings with mannose acceptors **9** and **10** (Fig. 1). However, the reactions between the stannylene acetals of these acceptors and donors **1** and **6** only led to decomposed donor and unreacted acceptor after 72 h. The stannylene acetals of **9** and **10** were fully soluble in dichloromethane and the lack of reactivity may therefore be due to the structure of

Table 2
Regioselective glycosylation with glucose and galactose donors and acceptors



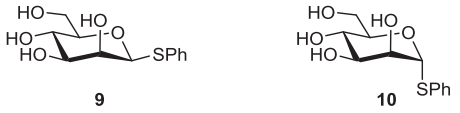
1: R^1 = OBn, R^2 = H
6: R^1 = H, R^2 = OBn
2: R^3 = OH, R^4 = H
4: R^3 = H, R^4 = OH



5: R^1 = OBn, R^4 = OH, R^2 = R^3 = H
7: R^2 = OBn, R^3 = OH, R^1 = R^4 = H
8: R^2 = OBn, R^4 = OH, R^1 = R^3 = H

Entry	Donor	Acceptor	Bu_2SnO (%)	Time (h)	Product	Yield (%)[a]
1	**1**	**4**	100	24	**5**	52
2	**1**	**4**	100	72	**5**	58
3	**1**	**4**	10	24	**5**	42
4	**1**	**4**	10	72	**5**	50
5	**6**	**2**	100	24	**7**	48
6	**6**	**2**	100	72	**7**	57
7	**6**	**2**	10	24	**7**	39
8	**6**	**2**	10	72	**7**	44
9	**6**	**4**	100	24	**8**	44
10	**6**	**4**	100	72	**8**	52
11	**6**	**4**	10	24	**8**	38
12	**6**	**4**	10	72	**8**	47

[a] Isolated yield of α(1 → 6)-linked disaccharides (none of the corresponding β-isomers were detected).

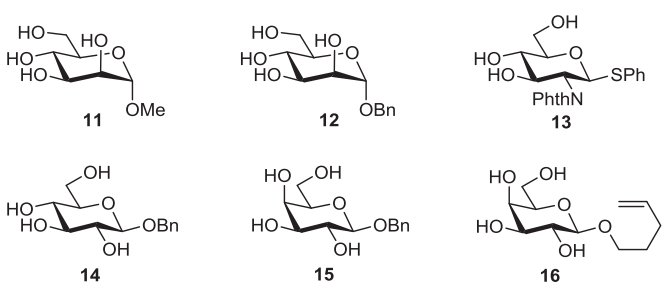


9 **10**

Fig. 1. Unreactive mannose acceptors.

the complexes. We have previously observed that mannose gives a lower yield than glucose and galactose in the regioselective Koenigs–Knorr glycosylation of the corresponding phenyl 1-thioglycosides.[5a] A similar difference between the three monosaccharides was observed in the Bu_2SnO-mediated *tert*-butyldimethylsilylation of the methyl glycosides at position 6.[15] These results may indicate that mannosides are less inclined to form a 4,6-stannylene acetal than glucosides and galactosides, but instead prefer a 2,3-acetal. Furthermore, these acetals can exist as dimers and oligomers in solution[16], which will probably render the stannylene complexes of **9** and **10** unreactive in the halide-mediated glycosylation.

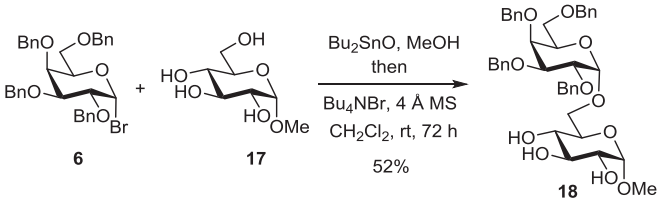
Acceptors **11**–**16** were also prepared (Fig. 2), but unfortunately the stannylene complexes of these were not soluble in



11 **12** **13**
14 **15** **16**

Fig. 2. Insoluble acceptors.

dichloromethane or THF. This was not a limitation with methyl α-D-glucopyranoside (**17**) which was fully dissolved after formation of the tin complex. As a result, glycosylation with donor **6** could be performed and disaccharide **18** was isolated in 52% yield after 72 h (Scheme 1). A mannose donor, i.e. tetra-*O*-benzyl-α-D-mannopyranosyl bromide, was also prepared, but no reaction occurred under the optimized conditions with acceptors **2** and **4**. This is not unexpected since this donor is known to be less reactive than **1** and **6** in the halide-mediated glycosylation.[17]



6 **17** **18**

Scheme 1. Regioselective glycosylation of **17**.

In summary, we have investigated the Bu_2SnO-directed glycosylation of 2,3,4,6-unprotected hexopyranosides with perbenzylated glycosyl bromide donors. Glucose and galactose acceptors can be employed if they are soluble in dichloromethane with Bu_2SnO while no coupling occurred with mannose acceptors. The same was observed with the donors where glucosyl and galactosyl bromides participated in the glycosylation while no conversion took place with the corresponding mannosyl bromide. With glucose and galactose donors and acceptors, the glycosylation occurred regioselectively at position 6 to afford the α-linked disaccharides in decent yields.

3. Experimental section

3.1. General methods

All reactions were performed under an argon atmosphere. Molecular sieves were flame-dried before use. Dichloromethane and tetrahydrofuran were taken from a PureSolv™ solvent purification system. Unprotected phenyl thioglycosides as well as benzyl and pent-4-enyl glycosides were synthesized according to literature procedures.[18] Tetrabutylammonium bromide was recrystallized from ethyl acetate and stored at 60 °C under high vacuum. TLC was performed on aluminum plates coated with silica gel 60. The plates were visualized with UV light or by dipping into a solution of cerium (IV) sulfate (2.5 g) and ammonium molybdate (6.25 g) in sulfuric acid (10%; 250 mL) followed by heating. Column chromatography was carried out with HPLC grade solvents on silica gel 60 (230–400 mesh). IR spectra were measured on a Bruker ALPHA-P FTIR spectrometer. NMR spectra were recorded on a Bruker Ascend instrument with a Prodigy cryoprobe. Chemical shifts were calibrated to the residual solvent signal in $CDCl_3$ (δ_H=7.26 ppm, δ_C=77.16 ppm) or to TMS. Assignment of ^1H and ^{13}C resonances were based on COSY, HSQC, and HMBC experiments. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. High resolution mass spectra were recorded on an Agilent 1100 LC system which was coupled to a Mircromass LCT orthogonal time-of-flight mass spectrometer.

3.2. Synthesis of glycosyl bromides 1 and 6

Oxalyl bromide (180 μL, 1.3 mmol) was added dropwise to a solution of the corresponding 2,3,4,6-tetra-*O*-benzyl-D-glycopyranose (540 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (10 mL). The reaction was stirred at room temperature for about 3 h until

disappearance of the starting material by TLC (EtOAc/heptane, 2:5). The mixture was then diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography (EtOAc/heptane, 2:5) to afford the pure glycosyl bromides as syrups (80% yield of **1** and 74% yield of **6**). NMR data were in accordance with literature values.[12]

3.3. General procedure for tin-mediated regioselective glycosylation

A suspension of the unprotected hexopyranoside (0.5 mmol) and Bu_2SnO (0.5 mmol) in MeOH (3.0 mL) was heated to reflux until a clear solution was obtained (3 h). The solvent was removed in vacuo followed by drying under high vacuum for 6 h to give the stannylene derivative as a colorless foam. The bromide donor (0.9 mmol) and 4 Å molecular sieves (300 mg) were then added to a solution of the stannylene derivative in CH_2Cl_2 (2 mL). The suspension was stirred at room temperature for 15 min. Tetrabutylammonium bromide (0.9 mmol) was then added and the mixture was stirred in the dark for the time indicated. The mixture was diluted with CH_2Cl_2, filtered and concentrated. The crude product was purified by column chromatography (toluene/acetone 3:1) or (CH_2Cl_2/MeOH 95:5 → 90:10) to afford the pure disaccharide.

3.4. Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1 → 6)-1-thio-β-D-glucopyranoside (3)

Colorless oil. R_f 0.54 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +0.8 (*c* 0.3, $CHCl_3$); ν_{max} (film) 3318, 1454, 1114, 1026, 836, 530 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.53–6.98 (m, 25H, Ar), 4.86 (d, *J*=10.9 Hz, 1H, OC*H*$_2$Ph), 4.74 (d, *J*=10.9 Hz, 1H, OC*H*$_2$Ph), 4.69 (d, *J*=10.9 Hz, 1H, OC*H*$_2$Ph), 4.67 (d, *J*=3.3 Hz, 1H, H-1′), 4.66 (d, *J*=10.9 Hz, 1H, OC*H*$_2$Ph), 4.54 (d, *J*=12.1 Hz, 1H, OC*H*$_2$Ph), 4.51 (d, *J*=12.1 Hz, 1H, OC*H*$_2$Ph), 4.43 (d, *J*=9.5 Hz, 1H, H-1), 4.39 (d, *J*=9.7 Hz, 1H, OC*H*$_2$Ph), 4.38 (d, *J*=9.7 Hz, 1H, OC*H*$_2$Ph), 4.02–3.79 (m, 2H, H-3′, H-6a), 3.78–3.35 (m, 9H, H-2′, H-3, H-5, H-5′, H-4, H-4′, H-6b, H-6a′, H-6b′), 3.24 (dd, *J*=9.0, 8.1 Hz, 1H, H-2); δ_C (100 MHz, $CDCl_3$) 138.7, 138.2, 137.9, 137.8, 132.9, 132–127 (Ar), 97.9 (C-1′), 88.1 (C-1), 82.1 (C-3′), 79.7 (C-2′), 77.6 (C-4′), 77.5 (C-3), 77.2 (C-5′), 75.8 (OCH_2Ph) 75.1 (OCH_2Ph), 73.5 (2×OCH_2Ph), 72.1 (C-5), 71.7 (C-2), 70.5 (C-4), 69.0 (C-6′), 68.5 (C-6); HRMS (ESI) calcd for $C_{46}H_{50}O_{10}S$ $[M+Na]^+$ *m*/*z* 817.3022, found 817.2997.

3.5. Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1 → 6)-1-thio-β-D-galactopyranoside (5)

Colorless oil. R_f 0.55 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +0.6 (*c* 0.4, $CHCl_3$); ν_{max} (film) 3452, 1452, 1141, 1025, 881, 740, 694 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.48–7.00 (m, 25H, Ar), 4.87 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 4.86 (d, *J*=3.7 Hz, 1H, H-1′), 4.75 (d, *J*=10.7 Hz, 1H, OC*H*$_2$Ph), 4.74 (d, *J*=10.7 Hz, 1H, OC*H*$_2$Ph), 4.70 (d, *J*=11.6 Hz, 1H, OC*H*$_2$Ph), 4.61 (d, *J*=11.9 Hz, 1H, OC*H*$_2$Ph), 4.52 (d, *J*=12.1 Hz, OC*H*$_2$Ph), 4.42 (d, *J*=9.7 Hz, 1H, H-1), 4.41 (d, *J*=12.1 Hz, 1H, OC*H*$_2$Ph), 4.37 (d, *J*=12.1 Hz, 1H, OC*H*$_2$Ph), 4.00–3.68 (m, 5H, H-3′, H-4′, H-5, H-6a, H-6b), 3.68–3.42 (m, 7H, H-2, H-2′, H-3, H-4, H-5′, H-6a′, H-6b′); δ_C (100 MHz, $CDCl_3$) 138.6, 138.2, 137.9, 137.8, 132.5, 132–127 (Ar), 98.0 (C-1′), 88.9 (C-1), 81.9 (C-3′), 79.6 (C-2′), 77.6 (C-5), 77.2 (C-4′), 75.7 (OCH_2Ph), 75.1 (OCH_2Ph) 74.7 (C-3), 73.5 (2×OCH_2Ph), 70.6 (C-5), 70.2 (C-2), 69.2 (C-4), 68.4 (C-6′), 67.8 (C-6); HRMS (ESI) calcd for $C_{46}H_{50}O_{10}S$ $[M+Na]^+$ *m*/*z* 817.3022, found 817.3004.

3.6. Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1 → 6)-1-thio-β-D-glucopyranoside (7)

Colorless oil. R_f 0.56 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +0.6 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3372, 2880, 1454, 1345, 1217, 1113, 1090, 967, 834, 749, 692 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.47–7.11 (m, 25H, Ar), 4.83 (d, *J*=11.4 Hz, 1H, OC*H*$_2$Ph), 4.75 (d, *J*=4.1 Hz, 1H, H-1′), 4.74 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 4.71 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 4.63 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 4.56 (d, *J*=11.9 Hz, 1H, OC*H*$_2$Ph), 4.46 (d, *J*=11.5 Hz, 1H, OC*H*$_2$Ph), 4.42 (d, *J*=9.7 Hz, 1H, H-1), 4.38 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 4.31 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 3.95 (dd, *J*=9.4, 3.8 Hz, 1H, H-2′), 3.93–3.82 (m, 3H, H-4′, H-5′, H-6a), 3.79 (dd, *J*=9.6, 3.5 Hz, 1H, H-3′), 3.51 (dd, *J*=10.3, 4.7 Hz, 1H, H-6b), 3.47–3.35 (m, 5H, H-3, H-4, H-5, H-6a′, H-6b′), 3.28–3.19 (m, 1H, H-2); δ_C (100 MHz, $CDCl_3$) 138.7, 138.5, 138.1, 137.7, 132.8, 130–127 (Ar), 98.5 (C-1′), 87.7 (C-1), 79.1 (C-3′), 77.6 (C-3), 77.3 (C-4′), 76.3 (C-2′), 74.8 (2×OCH_2Ph), 73.7 (C-5′), 73.5 (OCH_2Ph), 73.1 (OCH_2Ph), 72.0 (C-5), 71.7 (C-2), 69.7 (C-4), 69.1 (C-6′), 68.9 (C-6); HRMS calcd for $C_{46}H_{50}O_{10}S$ $[M+Na]^+$ *m*/*z* 817.3022, found 817.3026.

3.7. Phenyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1 → 6)-1-thio-β-D-galactopyranoside (8)

Colorless oil. R_f 0.54 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +0.9 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3423, 1453, 1113, 1025, 868, 743, 693 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.49–7.04 (m, 25H, Ar), 4.88 (d, *J*=3.7 Hz, 1H, H-1′), 4.83 (d, *J*=11.4 Hz, 1H, OC*H*$_2$Ph), 4.74 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 4.70 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 4.64 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 4.61 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 4.46 (d, *J*=11.4 Hz, 1H, OC*H*$_2$Ph), 4.39 (d, *J*=9.5 Hz, 1H, H-1), 4.37 (d, *J*=11.6 Hz, 1H, OC*H*$_2$Ph), 4.30 (d, *J*=11.7 Hz, 1H, OC*H*$_2$Ph), 3.96 (dd, *J*=9.4, 3.7 Hz, 1H, H-2′), 3.93–3.82 (m, 4H, H-2, H-4′, H-5′, H-6a), 3.78 (dd, *J*=9.6, 2.7 Hz, 1H, H-3′), 3.68 (dd, *J*=10.9, 5.3 Hz, 1H, H-6b), 3.59–3.37 (m, 5H, H-3, H-4, H-5, H-6a′, H-6b′); δ_C (100 MHz, $CDCl_3$) 138.6, 138.6, 138.1, 137.9, 132.8, 133–127 (Ar), 98.7 (C-1′), 88.6 (C-1), 78.9 (C-3′), 77.2 (C-2′), 76.2 (C-4′), 74.8 (C-3), 74.7 (C-5′), 73.8 (OCH_2Ph), 73.5 (OCH_2Ph), 72.9 (2×OCH_2Ph), 70.1 (C-5), 69.7 (C-2), 69.2 (C-4), 69.0 (C-6′), 67.8 (C-6); HRMS (ESI) calcd for $C_{46}H_{50}O_{10}S$ $[M+Na]^+$ *m*/*z* 817.3022, found 817.3012.

3.8. Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1 → 6)-α-D-glucopyranoside (18)

Colorless oil. R_f 0.51 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D$ +5 (*c* 0.6, $CHCl_3$); ν_{max} (film) 3381, 1452, 1114, 1024, 965, 546 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36–6.13 (m, 20H, Ar), 4.85 (d, *J*=11.5 Hz, 1H, OC*H*$_2$Ph), 4.77 (d, *J*=12.0 Hz, 1H, OC*H*$_2$Ph), 4.73 (d, *J*=11.5 Hz, 1H, OC*H*$_2$Ph), 4.71 (d, *J*=2.5 Hz, 1H, H-1′), 4.65 (d, *J*=11.6 Hz, 1H, OC*H*$_2$Ph), 4.64 (d, *J*=3.5 Hz, 1H, H-1), 4.58 (d, *J*=12.0 Hz, 1H, OC*H*$_2$Ph), 4.48 (d, *J*=11.6 Hz, 1H, OC*H*$_2$Ph), 4.40 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 4.30 (d, *J*=11.8 Hz, 1H, OC*H*$_2$Ph), 3.96 (dd, *J*=9.4, 3.8 Hz, 1H, H-2′), 3.90–3.80 (m, 4H, H-2, H-3, H-3′, H-6a), 3.67–3.58 (m, 2H, H-4, H-4′), 3.52–3.31 (m, 5H, H-5, H-5′, H-6b, H-6a′, H-6b′), 3.29 (s, 3H, OCH_3); δ_C (100 MHz, $CDCl_3$) 138.6, 138.5, 138.3, 137.6, 133–127 (Ar), 99.1 (C-1), 98.8 (C-1′), 79.1 (C-3′), 76.2 (C-2), 74.8 (C-3), 74.7 (C-4′), 74.3 (OCH_2Ph), 73.8 (OCH_2Ph), 73.6 (OCH_2Ph), 73.1 (OCH_2Ph), 72.3 (C-5), 72.0 (C-5′), 70.0 (C-2′), 69.4 (C-4), 69.3 (C-6′), 69.2 (C-6); HRMS (ESI) calcd for $C_{41}H_{48}O_{11}$ $[M+Na]^+$ *m*/*z* 739.3094, found 739.3082.

Acknowledgements

We thank The Novo Nordisk Foundation for financial support.

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of all compounds) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.11.059.

References and notes

1. (a) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934; (b) Smoot, J. T.; Demchenko, A. V. *Adv. Carbohydr. Chem. Biochem.* **2009**, *62*, 161–250.
2. (a) Calin, O.; Eller, S.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 5862–5865; (b) Ishiwata, A.; Ito, Y. *J. Am. Chem. Soc.* **2011**, *133*, 2275–2291; (c) Joe, M.; Bai, Y.; Nacario, R. C.; Lowary, T. L. *J. Am. Chem. Soc.* **2007**, *129*, 9885–9901; (d) Fraser-Reid, B.; Lu, J.; Jayaprakash, K. N.; López, J. C. *Tetrahedron: Asymmetry* **2006**, *17*, 2449–2463.
3. Böttcher, S.; Thiem, J. *Curr. Org. Chem.* **2014**, *18*, 1804–1817.
4. (a) Uriel, C.; Gómez, A. M.; López, J. C.; Fraser-Reid, B. *Org. Biomol. Chem.* **2012**, *10*, 8361–8370; (b) Yu, B.; Li, B.; Xing, G.; Hui, Y. *J. Comb. Chem.* **2011**, *3*, 404–406; (c) Kanie, O.; Barresi, F.; Ding, Y.; Labbe, J.; Otter, A.; Fosberg, L. S.; Ernst, B.; Hindsgaul, O. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2720–2722.
5. (a) Maggi, A.; Madsen, R. *Eur. J. Org. Chem.* **2013**, 2683–2691; (b) Kaji, E.; Harita, N. *Tetrahedron Lett.* **2000**, *41*, 53–56; (c) Garegg, P. J.; Maloisel, J.-L.; Oscarson, S. *Synthesis* **1995**, 409–414; (d) Cruzado, C.; Bernabe, M.; Martin-Lomas, M. *Carbohydr. Res.* **1990**, *203*, 296–301; (e) Murase, T.; Kartha, K. P. R.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1989**, *195*, 134–137.
6. Muramatsu, W.; Yoshimatsu, H. *Adv. Synth. Catal.* **2013**, *355*, 2518–2524.
7. (a) Fenger, T. H.; Madsen, R. *Eur. J. Org. Chem.* **2013**, 5923–5933; (b) Nishino, T.; Ohya, Y.; Murai, R.; Shirahata, T.; Yamamoto, D.; Makino, K.; Kaji, E. *Heterocycles* **2012**, *84*, 1123–1140.
8. Kaji, E.; Yamamoto, D.; Shirai, Y.; Ishige, K.; Arai, Y.; Shirahata, T.; Makino, K.; Nishino, T. *Eur. J. Org. Chem.* **2014**, 3536–3539.
9. Gouliaras, C.; Lee, D.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 13926–13929.
10. Reference 9 also contains one example where methyl 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-mannopyranoside is selectively glycosylated at position 6 of the mannose residue in the presence of the borinic acid catalyst.
11. Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.
12. The quality of oxalyl bromide proved important for fast and clean formation of **1** and it is recommended to use a freshly distilled sample. Previous syntheses of **1** with oxalyl bromide have also included DMF in the reaction, but in our hands the bromination worked equally well in the absence of the amide. See also: (a) Matwiejuk, M.; Thiem, J. *Eur. J. Org. Chem.* **2011**, 5860–5878; (b) Presser, A.; Kunert, O.; Pötschger, I. *Monatsh. Chem.* **2006**, *137*, 365–374; (c) Grayson, E. J.; Ward, S. J.; Hall, A. L.; Rendle, P. M.; Gamblin, D. P.; Batsanov, A. S.; Davis, B. G. *J. Org. Chem.* **2005**, *70*, 9740–9754; (d) Wessel, H.-P.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2251–2260.
13. Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4069–4075.
14. Kartha, K. P. R.; Aloui, M.; Field, R. A. *Tetrahedron Lett.* **1996**, *37*, 8807–8810.
15. Bredenkamp, M. W. *S. Afr. J. Chem.* **1995**, *48*, 154–156.
16. Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 17–142.
17. Rachaman, E. S.; Eby, R.; Schuerch, C. *Carbohydr. Res.* **1978**, *67*, 147–161.
18. (a) Schmidt, T. H.; Madsen, R. *Eur. J. Org. Chem.* **2007**, 3935–3941; (b) Clausen, M. H.; Jørgensen, M. R.; Thorsen, J.; Madsen, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 543–551; (c) Pedretti, V.; Veyrières, A.; Sinaÿ, P. *Tetrahedron* **1990**, *46*, 77–88.